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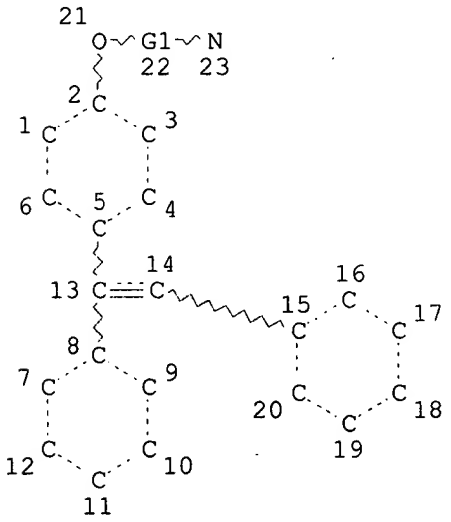


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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  23

STEREO ATTRIBUTES: NONE
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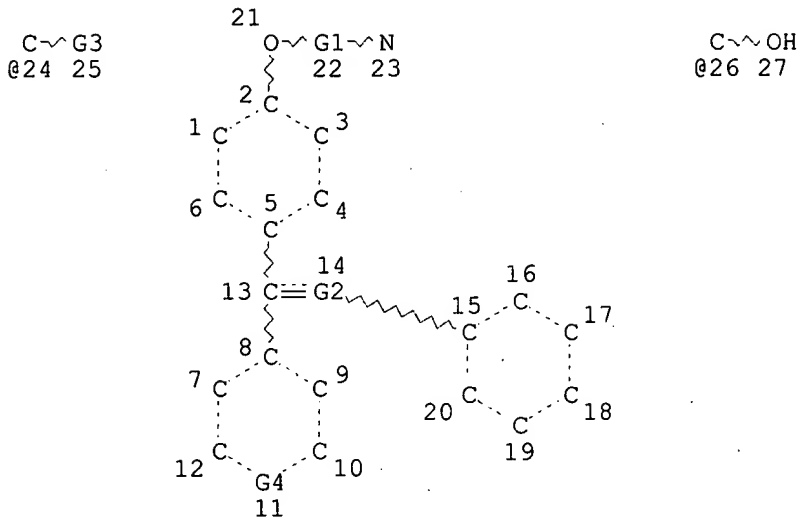
L6 STR



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NODE ATTRIBUTES:
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

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RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 27

STEREO ATTRIBUTES: NONE
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L8 4553 SEA FILE=HCAPLUS ABB=ON PLU=ON L7
L9 52 SEA FILE=HCAPLUS ABB=ON PLU=ON L8(L)(ENDOTHEL? OR MUSCLE)

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=> d ibib abs hitrn 19 1-52

L9 ANSWER 1 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:161506 HCAPLUS
DOCUMENT NUMBER: 134:202697
TITLE: Prevention and treatment of cardiovascular pathologies with tamoxifen analogues
INVENTOR(S): Grainger, David J.; Metcalfe, James C.; Kunz, Lawrence L.; Schroff, Robert W.
PATENT ASSIGNEE(S): NeoRx Corporation, USA
SOURCE: U.S., 48 pp., Cont.-in-part of U.S. Ser. No. 478,936, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6197789	B1	20010306	US 1997-973570	19971205

US 5595722	A	19970121	US 1995-476735	19950607
US 5770609	A	19980623	US 1995-486334	19950607
WO 9640098	A2	19961219	WO 1996-US10211	19960607
WO 9640098	A3	19970619		

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG

RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA

PRIORITY APPLN. INFO.:

US 1995-476735	A2	19950607
US 1995-477393	A2	19950607
US 1995-478936	B2	19950607
US 1995-486334	A2	19950607
WO 1996-US10211	W	19960607
US 1993-11669	B2	19930128
US 1993-61714	B2	19930513
US 1993-62451	B2	19930513
US 1994-241844	A2	19940512
US 1994-242161	A2	19940512

OTHER SOURCE(S): MARPAT 134:202697

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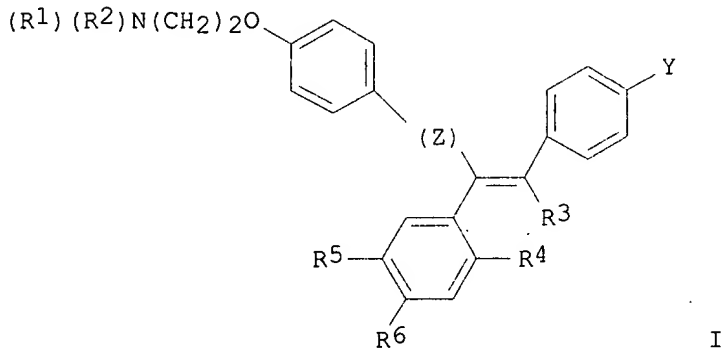

I

AB A method for treating or preventing cardiovascular pathologies by administering a compd. of the formula (I): wherein Z is C:O or a covalent bond; Y is H or O(C1-C4)alkyl, R1 and R2 are individually (C1 -C4)alkyl or together with N are a satd. heterocyclic group, R3 is Et or chloroethyl, R4 is H, R5 is I, O(C1 -C4)alkyl or H and R6 is I, O(C1 -C4)alkyl or H with the proviso that when R4, R5, and R6 are H, R3 is not ethyl; or a pharmaceutically acceptable salt thereof, effective to elevate the level of TGF-beta to treat and/or prevent conditions such as atherosclerosis, thrombosis, myocardial infarction, and stroke is provided. Useful compds. include idoxifene, toremifene or salts thereof. Further provided is a method for identifying an agent that elevates the level of TGF-beta. Another embodiment of the invention is an assay or kit to det. TGF-beta in vitro. Also provided is a therapeutic method comprising inhibiting smooth muscle cell proliferation assocd. with procedural vascular trauma employing the administration of tamoxifen or structural analogs thereof, including compds. of formula (I).

IT **10540-29-1D**, Tamoxifen, analogs **82413-20-5**, Droloxifene **116057-76-2**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention and treatment of cardiovascular pathol. with tamoxifen analogs and inhibition of vascular smooth **muscle** proliferation in relation to elevation of TGF beta)

REFERENCE COUNT: 28
REFERENCE(S): (2) Anon; EP 0054168 1982 HCAPLUS
(3) Anon; EP 054168 A1 1982 HCAPLUS

(4) Anon; DE 4401554 1994 HCAPLUS
(5) Anon; DE 4320896 1995 HCAPLUS
(6) Anon; DE 4320898 1995 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:137173 HCAPLUS
DOCUMENT NUMBER: 134:178396
TITLE: Synthesis, activity and formulations of pharmaceutical compounds for treatment of oxidative stress and/or endothelial dysfunction
INVENTOR(S): Del Soldato, Piero
PATENT ASSIGNEE(S): Nicox S.A., Fr.
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012584	A2	20010222	WO 2000-EP7225	20000727

W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: IT 1999-MI1817 A 19990812
OTHER SOURCE(S): MARPAT 134:178396
AB Compds. or their salts of general formula (I): A-B-N(O)s wherein: s is an integer equal to 1 or 2; A = R-T1-, wherein R is the drug radical and T1 = (CO)t or (X)t', wherein X = O, S, NR1c, R1c is H or a linear or branched alkyl or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1; B = -TB -X2-O- wherein TB = (CO) when t = 0, TB = X when t' = 0, X being as above defined; X2, bivalent radical, is such that the precursor drug of A and the precursor of B meet resp. the pharmacol. tests described in the description. Synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction are disclosed. The precursors are such as to meet the pharmacol. test reported in the description.
IT **82413-20-5**, Droloxifene
RL: RCT (Reactant)
(antitumor; synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or **endothelial** dysfunction)

L9 ANSWER 3 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:812730 HCAPLUS
DOCUMENT NUMBER: 134:13481
TITLE: Vascular endothelial growth factor is modulated in vascular muscle cells by estradiol, tamoxifen, and hypoxia
AUTHOR(S): Bausero, P.; Ben-Mahdi, M.-H.; Mazucatelli, J.-P.; Bloy, C.; Perrot-Applanat, M.
CORPORATE SOURCE: Remodelage Vasculaire, Institut National de la Sante et de la Recherche Medicale U460, Centre Hospitalier Universitaire Xavier Bichat, Paris, 75870, Fr.
SOURCE: Am. J. Physiol. (2000), 279(5, Pt. 2), H2033-H2042
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Vascular endothelial growth factor (VEGF) promotes neovascularization, microvascular permeability, and endothelial proliferation. We described previously VEGF mRNA and protein induction by estradiol (E2) in human endometrial fibroblasts. We report here E2 induction of VEGF expression in human venous muscle cells [smooth muscle cells (SMC) from human saphenous veins; HSVSMC] expressing both ER-.alpha. and ER-.beta. estrogen receptors. E2 at 10-9 to 10-8 M increases VEGF mRNA in HSVSMC in a time-dependent manner (3-fold at 24 h), as analyzed by semiquant. RT-PCR. This level of induction is comparable with E2 endometrial induction of VEGF mRNA. Tamoxifen and hypoxia also increase HSVSMC VEGF mRNA expression over control values. Immunocytochem. of saphenous veins and isolated SMC confirms translation of VEGF mRNA into protein. Immunoblot anal. of HSVSMC-conditioned medium detects three bands of 18, 23, and 28 kDa, corresponding to VEGF isoforms of 121, 165, and 189 amino acids. Radioreceptor assay of the conditioned medium produced by E2-stimulated HSVSMC reveals an increased VEGF secretion. Our data indicate that VEGF is E2, tamoxifen, and hypoxia inducible in cultured HSVSMC and E2 inducible in aortic SMC, suggesting E2 modulation of VEGF effects in angiogenesis, vascular permeability, and integrity.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(VEGF modulated in vascular **muscle** cells by estradiol and tamoxifen and hypoxia)

REFERENCE COUNT: 58
REFERENCE(S):
(1) Adams, M; Arteriosclerosis 1990, V10, P1051 HCAPLUS
(2) Banai, S; Cardiovasc Res 1994, V28, P1176 HCAPLUS
(3) Bausero, P; Angiogenesis 1998, V2, P167 HCAPLUS
(4) Bayard, F; Endocrinology 1995, V136, P1523 HCAPLUS
(5) Beato, M; Ann NY Acad Sci 1996, V784, P93 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:779730 HCAPLUS
DOCUMENT NUMBER: 134:95300
TITLE: Tamoxifen acutely relaxes coronary arteries by an endothelium-, nitric oxide-, and estrogen receptor-dependent mechanism
AUTHOR(S): Figtree, Gemma A.; Webb, Carolyn M.; Collins, Peter
CORPORATE SOURCE: Cardiac Medicine, National Heart and Lung Institute, Imperial College School of Medicine, London, UK
SOURCE: J. Pharmacol. Exp. Ther. (2000), 295(2), 519-523
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In epidemiol. studies tamoxifen has been assocd. with a redn. in the incidence of fatal myocardial infarction in women. However, the effects of tamoxifen on coronary artery reactivity are unknown. We hypothesized that tamoxifen would relax precontracted isolated rabbit coronary arteries. Rings of coronary artery from adult male and nonpregnant female New Zealand White rabbits were suspended in organ baths contg. Krebs' soln.; isometric tension was measured. Tamoxifen (0.1-100 .mu.M) induced significant endothelium-dependent relaxation in precontracted rabbit coronary arteries. This relaxation was inhibited by N.omega.-nitro-L-arginine Me ester and the estrogen receptor antagonist ICI 182,780. There was no significant effect on calcium concn.-dependent contraction curves. These data suggest that tamoxifen has beneficial effects on coronary reactivity that could, at least in part, account for the redn. in risk of fatal myocardial infarction in women taking tamoxifen.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tamoxifen acutely relaxes coronary arteries by **endothelium-**,

nitric oxide-, and estrogen receptor-dependent mechanism)
REFERENCE COUNT: 30
REFERENCE(S): (3) Chen, Z; J Clin Invest 1999, V103, P401 HCAPLUS
(5) Collins, P; Nat Med 1999, V5, P1130 HCAPLUS
(7) Figtree, G; Circulation 1999, V100, P1095 HCAPLUS
(8) Grainger, D; Nat Med 1995, V1, P1067 HCAPLUS
(9) Gustafsson, J; Nat Med 1997, V3, P493 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:742057 HCAPLUS
DOCUMENT NUMBER: 133:309791
TITLE: Synthesis, activity and formulations of pharmaceutical compounds for treatment of oxidative stress and/or endothelial dysfunction
INVENTOR(S): Del Soldato, Piero
PATENT ASSIGNEE(S): Nicox S.A., Fr.
SOURCE: PCT Int. Appl., 140 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061541	A2	20001019	WO 2000-EP3239	20000411

W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: IT 1999-MI752 A 19990413
OTHER SOURCE(S): MARPAT 133:309791
AB Synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction are disclosed. The precursors are such as to meet the pharmacol. test reported in the description.
IT **82413-20-5**, Droloxifene
RL: RCT (Reactant)
(antitumor; synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or **endothelial** dysfunction)

L9 ANSWER 6 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:608566 HCAPLUS
DOCUMENT NUMBER: 133:172188
TITLE: Methods to reduce the sensitivity of endothelially-compromised vascular smooth muscle
INVENTOR(S): Lamb, Fred S.
PATENT ASSIGNEE(S): University of Iowa Research Foundation, USA
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050023	A2	20000831	WO 2000-US4892	20000226

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,

MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-121727 P 19990226
OTHER SOURCE(S): MARPAT 133:172188

AB The present invention discloses materials and methods useful to treat sensitivity of endothelially-compromised vascular smooth muscle. In one embodiment, CLC3 blockers, particularly compds. of formula I are used to treat sensitivity.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods to reduce sensitivity of **endothelially**-compromised vascular smooth **muscle** using CLC3 chloride channel blockers such as tamoxifen in relation to use of other agents)

L9 ANSWER 7 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:397641 HCAPLUS
DOCUMENT NUMBER: 133:118234
TITLE: Vascular endothelial growth factor (VEGF) in breast cancer: comparison of plasma, serum, and tissue VEGF and microvessel density and effects of tamoxifen
AUTHOR(S): Adams, Jacqueline; Carder, Pauline J.; Downey, Sarah; Forbes, Mary A.; MacLennan, Kenneth; Allgar, Victoria; Kaufman, Sarah; Hallam, Susan; Bicknell, Roy; Walker, James J.; Cairnduff, Fiona; Selby, Peter J.; Perren, Timothy J.; Lansdown, Mark; Banks, Rosamonde E.
CORPORATE SOURCE: Imperial Cancer Research Fund Cancer Medicine Research Unit, St James's University Hospital, Leeds, LS9 7TF, UK
SOURCE: Cancer Res. (2000), 60(11), 2898-2905
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The assessment of angiogenesis in breast cancer is of importance as a key indicator of survival and response to therapy. Circulating vascular endothelial growth factor (VEGF) measurements may provide a less subjective anal. than microvessel d. (MVD) or immunohistochem. anal. of VEGF expression; however, most studies have used serum, which is now known to largely reflect platelet-derived VEGF concns. This study examd. for the first time both plasma (VEGFp) and serum (VEGFs) VEGF concns. in 201 blood samples from pre- and postmenopausal healthy controls and from patients with benign breast disease, localized breast cancer, breast cancer in remission, or metastatic breast cancer and related these to other clinicopathol. markers. VEGFp but not VEGFs concns. of patients with localized disease were significantly elevated compared with normal controls. Patients with metastatic disease had higher VEGFp and VEGFs levels than normal controls, and higher VEGFp, but not VEGFs, than patients with benign disease and patients with localized disease. However, the highest VEGFp and VEGFs concns. were seen in patients in remission compared with normal controls. VEGFp concns. in patients in remission were also higher than in patients with benign disease or patients with localized disease. Tamoxifen treatment was significantly assocd. with higher circulating and platelet-derived VEGF levels. Circulating VEGF did not correlate with any clinicopathol. factor, including MVD or VEGF expression. VEGF expression was significantly correlated with estrogen receptor status and inversely correlated with tumor grade. MVD correlated with tumor size. Tamoxifen-induced increases in VEGF may be important in clin. prognosis or assocd. pathologies.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(vascular **endothelial** growth factor (VEGF) in breast cancer and comparison of plasma, serum, and tissue VEGF and microvessel d. and effects of tamoxifen)

REFERENCE COUNT: 69

REFERENCE(S):
(1) Agrawal, R; Clin Endocrinol 1999, V50, P101 HCAPLUS
(3) Anan, K; J Surg Oncol 1997, V66, P257 HCAPLUS
(7) Banks, R; Br J Cancer 1998, V77, P956 HCAPLUS
(8) Benoy, I; Eur J Cancer 1998, V34, P1298 HCAPLUS
(10) Charnock-Jones, D; Biol Reprod 1993, V48, P1120 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 52 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:307450 HCAPLUS

DOCUMENT NUMBER: 133:69172

TITLE: Estrogen receptors .alpha. and .beta.: Prevalence of estrogen receptor .beta. mRNA in human vascular smooth muscle and transcriptional effects

AUTHOR(S): Hodges, Yvonne K.; Tung, Lin; Yan, Xiang-Dong; Graham, J. Dinny; Horwitz, Kathryn B.; Horwitz, Lawrence D.

CORPORATE SOURCE: Divisions of Cardiology, University of Colorado Health Sciences Center, Denver, CO, 80262, USA

SOURCE: Circulation (2000), 101(15), 1792-1798
CODEN: CIRCAZ; ISSN: 0009-7322

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background-Estrogens have vascular effects through the activation of estrogen receptors (ERs). In addn. to ER.alpha., the first ER to be cloned, a second subtype called ER.beta. has recently been discovered. Methods and Results-Using a reverse-transcriptase polymerase chain reaction assay that employs the same primer pair to simultaneously amplify ER.alpha. and ER.beta. transcripts, we found that ER.beta. is the ER form that is predominantly expressed in human vascular smooth muscle, particularly in women. The transcriptional effects of the 2 ERs in transfected HeLa cells differed. In response to 17.beta.-estradiol, ER.alpha. is a stronger transactivator than ER.beta. at low receptor concns. However, at higher receptor concns., ER.alpha. activity self-squelches, and ER.beta. is a stronger transactivator. Tamoxifen has partial agonist effects with ER.alpha. but not with ER.beta.. Conclusions-The protective effects of estrogens in the cardiovascular system of women may be due to the genomic effects of ER.beta. in vascular tissue.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(tamoxifen has partial agonist effects with ER.alpha. but not with ER.beta. in vascular smooth **muscle**)

REFERENCE COUNT: 29

REFERENCE(S):
(2) Brzozowski, A; Nature 1997, V389, P753 HCAPLUS
(3) Chaidarun, S; J Clin Endocrinol Metab 1998, V83, P3308 HCAPLUS
(4) Chen, S; Circulation 1996, V93, P577 HCAPLUS
(5) Hodges, Y; Circulation 1999, V99, P2688 HCAPLUS
(6) Horwitz, K; J Clin Invest 1982, V69, P750 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 9 OF 52 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:158715 HCAPLUS

DOCUMENT NUMBER: 132:260835

TITLE: Estrogen modulates a large conductance chloride channel in cultured porcine aortic endothelial cells

AUTHOR(S): Li, Zhiyuan; Niwa, Yasuharu; Sakamoto, Sadaichi; Chen, Xiu; Nakaya, Yutaka

CORPORATE SOURCE: Department of Nutrition, School of Medicine, Tokushima

University, Tokushima, 770, Japan
SOURCE: J. Cardiovasc. Pharmacol. (2000), 35(3), 506-510
CODEN: JCPCDT; ISSN: 0160-2446
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Estrogen is known to exert a protective effect on cardiovascular disease, but the mechanism for this effect is unclear. It has, however, been reported that estrogen and antiestrogen modify ionic currents and membrane potential in various cells. The aim of this study was to clarify whether the chloride channel of aortic endothelial cells was, in fact, modified by estrogen and antiestrogen with inside-out patch and cell-attached patch recording methods. Tamoxifen activated a large-conductance (368 pS, in sym. 150 mM Cl- soln.) chloride channel of endothelial cells grown in the presence of 1 .mu.g/mL colchicine. The channels were activated mainly between .+-. 40 mV, but were inactivated at more extreme potentials. The open probability of channels in cell-attached patches increased from <0.01 to 0.37 when cells were treated with 15 .mu.M tamoxifen. This effect can be blocked by 17.beta.-estradiol, but not by progesterone. The results showed that tamoxifen increased chloride channel activity in the presence of colchicine in cultured endothelial cells, and this action was suppressed by 17.beta.-estradiol but not by progesterone. This rapid effect by estrogens suggests that these hormones exert nongenomic, short-term activity and do not appear to affect the nuclear estrogen receptor. With these effects, estrogen and antiestrogen bind to the endothelial cells plasma membrane site and subsequently may activate an intracellular second messenger pathway.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(estrogen and antiestrogen modulate large conductance chloride channel in cultured porcine aortic **endothelial** cells)

REFERENCE COUNT: 34
REFERENCE(S):
(1) Blaustein, J; J Neuroendocrinol 1993, V5, P63 HCAPLUS
(2) Chen, Z; J Clin Invest 1999, V103, P401 HCAPLUS
(3) Delarue, F; Am J Physiol 1998, V275, PH1011 HCAPLUS
(5) Fernandez, A; Gen Pharmacol 1993, V24, P391 HCAPLUS
(6) Furchgott, R; Circ Res 1983, V53, P557 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 52 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:39761 HCAPLUS
DOCUMENT NUMBER: 132:303070

TITLE: The inhibitory action of tamoxifen on the contraction of Ascaris suum somatic muscle in response to acetylcholine

AUTHOR(S): Trim, N.; Holden-Dye, L.; Walker, R. J.
CORPORATE SOURCE: School of Biological Sciences, University of Southampton, Southampton, SO16 7PX, UK

SOURCE: Parasitology (1999), 119(6), 655-662
CODEN: PARAAE; ISSN: 0031-1820
PUBLISHER: Cambridge University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The somatic muscle of Ascaris suum is principally under the excitatory control of the neuromuscular junction transmitter, acetylcholine (ACh). However, it has recently been shown that neuropeptides also play an important role in the motor-nervous system and one of these, AF3 (AVPGVLRFamide), also contracts muscle. The events which trigger contraction to ACh and AF3 would appear to be different, with ACh activating a nicotinic acetylcholine receptor while the response to AF3 is most likely to involve a G-protein-coupled receptor neg. coupled to adenylate cyclase. In order to further elucidate differences in the

cellular signalling pathways through which ACh and AF3 elicit muscle contraction, the authors investigated the actions of protein kinase C inhibitors, tamoxifen and chelerythrine, on the dorsal somatic muscle strip of A. suum. Contractions in response to 1 .mu.M AF3 were potentiated by 17% in the presence of 10 .mu.M tamoxifen ($P < 0.05$; n = 8); however, contractions in response to 10 .mu.M ACh were markedly inhibited (tamoxifen IC50 44 .+-. 18 .mu.M; n = 6). Tamoxifen also blocked muscle cell depolarizations to 5 .mu.M ACh (IC50 4 .+-. 1 .mu.M; n = 6) and 1 .mu.M levamisole (IC50 14 .+-. 6 .mu.M; n = 4). This was unlikely to be a non-specific effect on the membrane as hyperpolarizations to 10 .mu.M GABA were unaffected (93% of control with 10 .mu.M tamoxifen; n = 6; $P > 0.05$). However, another inhibitor of mammalian protein kinase C, chelerythrine, did not affect the response either to ACh or AF3 (n = 6).

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitory action of tamoxifen on contraction of Ascaris suum somatic **muscle** in response to acetylcholine)

REFERENCE COUNT: 28
REFERENCE(S):
(1) Ajùh, P; Gene 1994, V144, P127 HCAPLUS
(2) Arevalo, J; Molecular and Biochemical Parasitology 1991, V48, P151 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:602841 HCAPLUS
DOCUMENT NUMBER: 131:297859
TITLE: Effects of anion channel antagonists in canine colonic myocytes: comparative pharmacology of Cl-, Ca2+ and K+ currents
AUTHOR(S): Dick, Gregory M.; Kong, In Deok; Sanders, Kenton M.
CORPORATE SOURCE: Department of Physiology & Cell Biology, University of Nevada School of Medicine, Reno, NV, 89557, USA
SOURCE: Br. J. Pharmacol. (1999), 127(8), 1819-1831
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 1 Vol.-Sensitive, Outwardly Rectifying (VSOR) Cl- currents were measured in canine colonic myocytes by whole-cell patch clamp. Decreasing extracellular osmolarity 50 milliosmoles l-1 activated current that was carried by Cl- and 5-7 times greater in the outward direction. 2 Niflumic acid, an inhibitor of Ca2+-activated Cl- channels, did not inhibit VSOR Cl- current. Glibenclamide, an antagonist of CFTR, and anthracene-9-carboxylate (9-AC) inhibited current less than 25% at 100 .mu.M. 3 DIDS (4,4-diisothiocyanato-stilbene-2,2'disulfonate) inhibited VSOR Cl- current more potently than SITS (4-acetamido-4'-isothiocyanato-stilbene-2,2'-disulfonate). IC50s were 0.84 and 226 .mu.M, resp. 4 VSOR Cl- current was strongly inhibited by tamoxifen ([Z]-1-[p-dimethylaminoethoxy-phenyl]-1,2-diphenyl-1-butene), an anti-estrogen compd. (IC50=0.57 .mu.M). 5 Gd3+ antagonized VSOR Cl- current more potently than La3+. The IC50 for Gd3- was 23 .mu.M. In contrast, 100 .mu.M La3+ inhibited current only 35.+-.7%. 6 Antagonists of VSOR Cl- current had non-specific effects. These compds. blocked voltage-dependent K+ and Ca2+ currents in colonic myocytes. Tamoxifen (10 .mu.M) and DIDS (10 .mu.M) inhibited L-type Ca2+ current 87.+-.7 and 31.+-.5%, resp. Addnl., in the presence of 300 nM charybdotoxin, tamoxifen (1 .mu.M) and DIDS (10 .mu.M) inhibited delayed rectifier K+ current 38.+-.8 and 10.+-.2%, resp. 7 The pharmacol. of VSOR Cl- channels overlaps with voltage-dependent cation channels. DIDS and tamoxifen inhibited VSOR Cl-

equally. However, because DIDS had much less effect on L-type Ca2+ and delayed rectifier K+ channels than did tamoxifen, it might be useful in expts. to investigate the physiol. and pathophysiol. role of this conductance in whole tissues.

IT **10540-29-1**, Tamoxifen
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(comparative pharmacol. of chloride, calcium, and potassium currents in colon **muscle**: channel antagonists as tools)

REFERENCE COUNT: 47
REFERENCE(S):
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(13) Duan, D; J Gen Physiol 1999, V113, P57 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:534801 HCAPLUS
DOCUMENT NUMBER: 131:309369
TITLE: Reduced expression of endothelial and inducible nitric oxide synthase in a human breast cancer cell line which has acquired estrogen independence
AUTHOR(S): Martin, J. H. J.; Alalami, O.; van den Berg, H. W.
CORPORATE SOURCE: Division of Biomedical Sciences, University of Wolverhampton, Wolverhampton, UK
SOURCE: Cancer Lett. (Shannon, Irel.) (1999), 144(1), 65-74
CODEN: CALEDQ; ISSN: 0304-3835
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have recently reported the presence of inducible nitric oxide synthase (iNOS) in the human breast cancer cell line ZR-75-1. The purpose of the present study was to examine differences in expression of endothelial (eNOS) and inducible nitric oxide synthase in normal human mammary epithelial cells (HMEC) compared with two variants of the ZR-75-1 cell line. One variant has acquired estrogen independence, the other has acquired resistance to tamoxifen. Immunohistochem. investigations demonstrated that 100% of HMEC cells staining pos. for both eNOS and iNOS. ZR-75-1 cells showed 100% staining for eNOS and 52% pos. staining for iNOS. There was no difference in staining between the parent cell line and cells which had acquired resistance to tamoxifen (ZR-75-9a1). However, in the breast cancer cell line which had acquired estrogen independence (ZR-PR-LT), less than 5% of cells exhibited pos. staining for eNOS and staining for iNOS was undetectable. L-Arginine increased NO prodn. in both ZR-75-9a1 and ZR-PR-LT cells. Progesterone was able to down regulate NO prodn. in both ZR-75-1 and ZR-75-9a1 cells and this effect was reversible by RU486. These results support the suggestion that loss of NOS expression may be assocd. with the progression of breast cancers.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**endothelial** and inducible nitric oxide synthase expression in human breast cancer in relation to estrogen independence and tamoxifen resistance)

REFERENCE COUNT: 25
REFERENCE(S):
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(2) Andrade, S; Br J Pharmacol 1992, V107, P1092 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:489047 HCAPLUS

DOCUMENT NUMBER: 131:238124
TITLE: Inhibition of estrogen receptor function promotes porcine coronary artery smooth muscle cell proliferation
AUTHOR(S): Lavigne, Mark C.; Ramwell, Peter W.; Clarke, Robert
CORPORATE SOURCE: Department of Physiology and Biophysics, Vincent T. Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC, 20007, USA
SOURCE: Steroids (1999), 64(7), 472-480
CODEN: STEDAM; ISSN: 0039-128X
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Estradiol-17.beta. (E2) can inhibit vascular smooth muscle cell (VSMC) proliferation probably through its ability to activate its nuclear estrogen receptors (ER). Activation or inhibition of the ER by cognate permissive or non-permissive ligands, resp., would indicate whether ER action is crit. for this vascular protective effect. We investigated a previously characterized population of cultured porcine coronary artery SMCs for ER expression and for the response of these cells to estrogens and antiestrogens. Reverse transcription-polymerase chain reaction and Western blot analyses demonstrated ER mRNA and protein, resp., in these cells. While the culture conditions required may have prevented the demonstration of physiol. effects of E2, the antiestrogens, ICI 182780 and 4-hydroxytamoxifen, stimulated VSMC proliferation. The data suggest that, by interrupting ER function, antiestrogens significantly increased the VSMC mitotic rate. This model may be used to identify ER-regulated genes that function to control the growth of these coronary artery SMCs.

IT **68047-06-3**, 4-Hydroxytamoxifen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(estrogen receptor function inhibition promotion of porcine coronary artery smooth **muscle** cell proliferation)

REFERENCE COUNT: 47
REFERENCE(S):
(1) Adams, M; Transplantation Proc 1989, V21, P3662 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 14 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:380179 HCAPLUS
DOCUMENT NUMBER: 131:139246
TITLE: Tissue-selective expression of dominant-negative proteins for the regulation of vascular smooth muscle cell proliferation
AUTHOR(S): Schmitt, J. F.; Keogh, M.-C.; Dennehy, U.; Chen, D.; Lupu, F.; Weston, K.; Taylor, D.; Kakkar, V. V.; Lemoine, N. R.
CORPORATE SOURCE: Thrombosis Research Institute, Molecular Oncology Unit, Imperial College School of Medicine, London, UK
SOURCE: Gene Ther. (1999), 6(6), 1184-1191
CODEN: GETHEC; ISSN: 0969-7128
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The transcription factors c-myb and c-myc are essential for vascular smooth muscle cell (VSMC) replication and are rapidly induced following mitogenic stimulation of quiescent VSMCs in vitro and in vivo following balloon catheter injury. Consequently, interference with c-myb and c-myc function provide a possible avenue for the prevention of VSMC proliferation assocd. with intimal hyperplasia. We have carried out studies focused on the inhibition of VSMC proliferation using

dominant-neg. gene constructs incorporating the DNA-binding domains of the c-myb or c-myc genes fused to the repressor domain of the Drosophila engrailed gene. Transient transfection of rat, rabbit and human vascular SMCs results in a dramatic inhibition of proliferation for at least 72 h after transfection. Furthermore, this inhibition of cellular proliferation was found to be due, at least in part, to the induction of apoptosis. Coupling expression of the chimeric dominant-neg. proteins to transcriptional regulatory elements of the human vascular smooth muscle .alpha.-actin gene allows specific targeting of vascular smooth muscle cells.

IT **68047-06-3**, 4-Hydroxytamoxifen
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(tissue-selective expression of dominant-neg. proteins for the regulation of vascular smooth **muscle** cell proliferation)

REFERENCE COUNT: 49
REFERENCE(S):
(1) Amati, B; Cell 1993, V72, P233 HCAPLUS
(2) Amati, B; Curr Opin Genet Dev 1994, V4, P102 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 15 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:255934 HCAPLUS
DOCUMENT NUMBER: 131:28126
TITLE: Short-term exposure to physiological levels of 17.beta.-estradiol enhances endothelium-independent relaxation in porcine coronary artery
AUTHOR(S): Teoh, Hwee; Leung, Susan W. S.; Man, Ricky Y. K.
CORPORATE SOURCE: Department of Pharmacology, Faculty of Medicine, The University of Hong Kong, Hong Kong
SOURCE: Cardiovasc. Res. (1999), 42(1), 224-231
CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB While alterations in cholesterol and lipoprotein profiles partly account for menopause being a risk factor for coronary heart disease, recent studies have suggested that 17.beta.-estradiol may have vascular effects. The authors' aims were to study the short-term effects of 17.beta.-estradiol on vascular function in isolated porcine coronary artery rings. Concomitantly, the authors sought to det. if physiol. concns. of 17.beta.-estradiol could acutely potentiate relaxation. 17.alpha.- And 17.beta.-estradiol at pharmacol. (>1 .mu.M) concns. produced relaxation in U46619-precontracted porcine coronary artery rings. Relaxation evoked by 17.beta.-estradiol was not reversed by the estrogen receptor antagonists tamoxifen and ICI 182780. Following 20 min exposure to a physiol. concn. of 17.beta.-estradiol (1 nM), which on its own had no effect, relaxation elicited by cromakalim, levcromakalim and sodium nitroprusside, but not bradykinin or calcium ionophore A23187, were significantly enhanced. This potentiating action was also insensitive to tamoxifen and ICI 182780. The authors' data provide evidence for an acute indirect relaxant action of 17.beta.-estradiol and suggest that it may be via a tamoxifen- and ICI 182780-insensitive estrogen receptor. While this response was only obsd. at pharmacol. concns., the potentiation of cromakalim, levcromakalim and sodium nitroprusside relaxation was evident in the presence of a physiol. concn. (1 nM) of 17.beta.-estradiol. These results demonstrate that short-term exposure to 17.beta.-estradiol, at concns. that have no effect on their own, can enhance vasorelaxation. These vascular effects may partly account for some of the acute effects of 17.beta.-estradiol on blood flow.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(estradiol enhances **endothelium**-independent relaxation in porcine coronary artery mediation by tamoxifen-insensitive estrogen receptors)

REFERENCE COUNT: 45
REFERENCE(S):
(3) Bell, D; Am J Physiol 1995, V268, PH377 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 16 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:104213 HCAPLUS
DOCUMENT NUMBER: 130:291387
TITLE: Selective estrogen receptor modulators: different actions on vascular cell adhesion molecule-1 (VCAM-1) expression in human endothelial cells
AUTHOR(S): Simoncini, T.; De Caterina, R.; Genazzani, A. R.
CORPORATE SOURCE: CNR Institute of Clinical Physiology, Pisa and Scuola Superiore S. Anna, Pisa (RDC), Department of Reproductive Medicine and Child Development, Division of Obstetrics and Gynecology, University of Pisa (TS, ARG), Pisa, Italy
SOURCE: J. Clin. Endocrinol. Metab. (1999), 84(2), 815-818
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Selective estrogen receptors modulators (SERMs) are a series of new compds. exerting estrogenic or anti-estrogenic effects in different tissues. 17.beta.-Estradiol is known to inhibit endothelial vascular cell adhesion mol. (VCAM)-1 expression. We studied the relative effects of the raloxifene analog LY117018 and of tamoxifen on lipopolysaccharide (LPS)-induced VCAM-1 expression in cultured human saphenous vein endothelial cells (HSVEC) and on HSVEC adhesiveness towards U937 monocytoid cells. We here demonstrate a concn.-dependent inhibitory action on VCAM-1 protein expression both for 17.beta.-estradiol and LY117018. The action of both compds. was blocked by the pure anti-estrogen ICI 182,780. LY117018 did not antagonize 17.beta.-estradiol activity. On the contrary, tamoxifen had no effects of his own. Both 17.beta.-estradiol and LY117018 inhibited HSVEC VCAM-1 expression at the mRNA level, while tamoxifen was ineffective. Finally, 17.beta.-estradiol and LY117018, but not tamoxifen, inhibited HSVEC adhesiveness towards U937 monocytoid cells induced by LPS stimulation. Therefore, only some SERMs have potential anti-atherogenic actions exerted directly at the vascular level through the regulation of endothelial cell adhesion mols. expression and of endothelial-leukocyte interactions.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(estrogen receptor modulators: different actions on VCAM-1 expression in vascular **endothelium**)

REFERENCE COUNT: 23
REFERENCE(S):
(5) Caulin-Glaser, T; J Clin Invest 1996, V98, P36 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 17 OF 52 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:94554 HCAPLUS
DOCUMENT NUMBER: 130:262316
TITLE: Estrogen and tamoxifen metabolites protect smooth muscle cell membrane phospholipids against peroxidation and inhibit cell growth
AUTHOR(S): Dubey, Raghvendra K.; Tyurina, Yulia Y.; Tyurin, Vladimir A.; Gillespie, Delbert G.; Branch, Robert A.; Jackson, Edwin K.; Kagan, Valerian E.
CORPORATE SOURCE: Center for Clinical Pharmacology and Department of Medicine, University of Pittsburgh, Pittsburgh, PA, 15213-2582, USA
SOURCE: Circ. Res. (1999), 84(2), 229-239
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The goal of this study was to test the hypothesis that antioxidant estrogens, by a mechanism independent of the estrogen receptor, protect phospholipids residing in the plasma membrane of vascular smooth muscle cells from peroxidn. and peroxidn.-induced cell growth and migration. Peroxidn. of membrane phospholipids was assessed by HPLC anal. of phospholipids extd. from rat aortic vascular smooth muscle cells prelabeled with cis-parinaric acid (a fatty acid that is susceptible to peroxidn., which quenches its fluorescent properties). Incubation of cells for 2 h with the peroxyl radical donor 2,2'-azobis-2,4-dimethylvaleronitrile (AMVN) caused peroxidn. of all measured membrane phospholipids. This effect was attenuated by pretreating cells for 15 min with 50 to 5000 ng/mL of 2-hydroxyestradiol (strong antioxidant but weak estrogen-receptor ligand) or 4-hydroxytamoxifen (strong antioxidant and potent estrogen-receptor ligand), but not by estrone or droloxifene (both weak antioxidants but potent estrogen-receptor ligands). Moreover, pretreatment of cells for 20 h with physiol. concns. (0.3 ng/mL) of 2-hydroxyestradiol or pharmacol. relevant concns. of 4-hydroxytamoxifen (40 ng/mL) also decreased AMVN-induced phospholipid peroxidn. Both 2-hydroxyestradiol and 4-hydroxytamoxifen were as effective as 2,2,5,7,8-pentamethyl-6-hydrochromane (an antioxidant homolog of vitamin E) in attenuating AMVN-induced peroxidn. of membrane phospholipids. Also, physiol. concns. of 2-hydroxyestradiol, but not estrone, and pharmacol. relevant concns. of 4-hydroxytamoxifen attenuated AMVM-induced DNA synthesis, cell proliferation, and cell migration. These studies demonstrate in vascular smooth muscle cells that antioxidant estrogens via a non-estrogen receptor-dependent mechanism attenuate peroxidn. of membrane phospholipids and peroxidn.-induced cell growth and migration.
IT **82413-20-5**, Droloxifene
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(estrogen and tamoxifen metabolites protect smooth **muscle** cell membrane phospholipids against peroxidn. and inhibit peroxidn.-induced cell growth and migration)
IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(estrogen and tamoxifen metabolites protect smooth **muscle** cell membrane phospholipids against peroxidn. and inhibit peroxidn.-induced cell growth and migration)
IT **68047-06-3**, 4-Hydroxytamoxifen
RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(estrogen and tamoxifen metabolites protect smooth **muscle** cell membrane phospholipids against peroxidn. and inhibit peroxidn.-induced cell growth and migration)
REFERENCE COUNT: 48
REFERENCE(S):
(1) Adlercreutz, H; J Natl Cancer Inst 1994, V86, P1076 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 18 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:797424 HCAPLUS
DOCUMENT NUMBER: 130:119964
TITLE: Transforming growth factor-.beta. dynamically regulates vascular smooth muscle differentiation in vivo
AUTHOR(S): Grainger, David J.; Metcalfe, James C.; Grace, Andrew A.; Mosedale, David E.
CORPORATE SOURCE: Department of Biochemistry, University of Cambridge, Cambridge, CB2 1QW, UK
SOURCE: J. Cell Sci. (1998), 111(19), 2977-2988
CODEN: JNCSAI; ISSN: 0021-9533
PUBLISHER: Company of Biologists Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Variations in the levels of smooth muscle-specific isoforms of contractile proteins have been reported to occur in many different vascular diseases. However, although much work has been done in vitro to investigate the regulation of smooth muscle cell differentiation, the mol. mechanisms which regulate the differentiation of vascular smooth muscle tissue in vivo are unknown. Using quant. immunofluorescence, we show that in rat arteries levels of smooth muscle differentiation markers correlate with the levels of the cytokine TGF-.beta.. In young mice with one allele of the TGF-.beta.1 gene deleted, the levels of both TGF-.beta.1 and smooth muscle differentiation markers are reduced compared to wild-type controls. This regulation of smooth muscle differentiation by TGF-.beta. during postnatal development also occurs dynamically in the adult animal. Following various pharmacol. or surgical interventions, including treatment of mice with tamoxifen and balloon injury of rat carotid arteries, there is a strong correlation between the changes in the levels of TGF-.beta. and changes in the levels of smooth muscle differentiation markers (r = 0.9). We conclude that TGF-.beta. dynamically regulates smooth muscle differentiation in rodent arteries in vivo.
IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(TGF-.beta. regulation of vascular smooth **muscle** differentiation after tamoxifen treatment of mice)
REFERENCE COUNT: 45
REFERENCE(S): (1) Aikawa, M; Circ Res 1993, V73, P1000 HCAPLUS
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(6) Cheifetz, S; J Biol Chem 1990, V265, P20533 HCAPLUS
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(9) Desmouliere, A; J Cell Biol 1993, V122, P103 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 19 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:788752 HCAPLUS
DOCUMENT NUMBER: 130:33027
TITLE: TGF-.beta. activators and TGF-.beta. production stimulators for prevention and treatment of pathologies associated with abnormally proliferative smooth muscle cells
Grainger, David J.; Metcalfe, James C.; Weissberg, Peter L.
NEE(S): NeoRx Corporation, USA
U.S., 25 pp., Cont.-in-part of U.S. Ser. No. 61,714,

abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5847007	A	19981208	US 1994-242161	19940512
CA 2162586	AA	19941124	CA 1994-2162586	19940512
US 5472985	A	19951205	US 1994-300357	19940902
US 5545569	A	19960813	US 1995-450520	19950525
US 5595722	A	19970121	US 1995-476735	19950607
US 5770609	A	19980623	US 1995-486334	19950607
US 5599844	A	19970204	US 1995-528810	19950915
US 5773479	A	19980630	US 1995-560808	19951121
US 5945456	A	19990831	US 1997-965254	19971106
US 6166090	A	20001226	US 1997-965589	19971106

PRIORITY APPLN. INFO.:
US 1993-61714 B2 19930513
US 1993-11669 B2 19930128
US 1993-62451 B2 19930513
US 1994-241844 A2 19940512
US 1994-242161 A3 19940512
US 1994-300357 A1 19940902
US 1995-560808 A1 19951121

AB TGF-.beta. activators and TGF-.beta. prodn. stimulators are employed to maintain or increase vessel lumen diam. in a diseased or injured vessel of a mammal. Conditions such as restenosis following angioplasty, vascular bypass grafts, transplanted organs, atherosclerosis or hypertension are characterized by a reduced vessel lumen diam. In a preferred embodiment of the invention, TGF-.beta. activators and prodn. stimulators inhibit abnormal proliferation of smooth muscle cells. TGF-.beta. activators or prodn. stimulators that are not characterized by an undesirable systemic toxicity profile at a prophylactic dose are also amenable to chronic use for prophylactic purposes with respect to disease states involving proliferation and/or migration of vascular smooth muscle cells over time. Further provided is a method for detg. TGF-.beta. in vitro, thereby identifying a patient at risk for atherosclerosis and monitoring a recipient that has received one or more administrations of a TGF-.beta. activator or prodn. stimulator.

IT **10540-29-1**, Tamoxifen **10540-29-1D**, Tamoxifen, analogs
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TGF-.beta. activators and TGF-.beta. prodn. stimulators for prevention and treatment of pathologies assocd. with abnormally proliferative smooth **muscle** cells)

REFERENCE COUNT: 57
REFERENCE(S):
(3) Anon; EP 0260066 1990 HCAPLUS
(4) Anon; EP 0365863 B1 1990 HCAPLUS
(5) Anon; EP 0374044 B1 1990 HCAPLUS
(7) Anon; EP 0542679 A1 1993 HCAPLUS
(8) Anon; EP 0584953 A1 1994 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 20 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:723716 HCAPLUS
DOCUMENT NUMBER: 128:70425
TITLE: Triphenylethylene antiestrogens induce uterine vascular endothelial growth factor expression via their partial estrogen agonist activity
AUTHOR(S): Hyder, Salman M.; Chiappetta, Constance; Stancel, George M.
CORPORATE SOURCE: TX, 6431 Fannin, PO Box 20708, Pharmacology and Physiology, Department of Integrative Biology, University of Texas Health Sciences Center -Houston,

Houston, 77225, USA
SOURCE: Cancer Lett. (Shannon, Irel.) (1997), 120(2), 165-171
CODEN: CALEDQ; ISSN: 0304-3835
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Estradiol induces vascular endothelial growth factor (VEGF) expression in the rat uterus and this may contribute to the hyperemia and increased vascularity produced by estrogens in this target tissue. Triphenylethylene antiestrogens such as tamoxifen have mixed agonist/antagonist activity and their specific effects are tissue and gene specific. These drugs exhibit primarily antiestrogenic actions in mammary tissue and are thus used for the treatment of breast cancer. These drugs are also suggested to be inhibitors of angiogenesis. However, uterine side effects of tamoxifen are thought to stem largely from the agonist activity of the drug in this tissue. Since side effects of tamoxifen such as uterine bleeding and endometrial cancer seem likely to have an angiogenic component, we have examd. the effects of this drug, its metabolite, 4-hydroxy-tamoxifen and two addnl. triphenylethylene antiestrogens, nafoxidine and clomiphene, on the expression of VEGF and another estrogen regulated gene, c-fos, using the rat uterus as an exptl. system. All four compds. increase uterine VEGF and c-fos mRNA levels indicating that the triphenylethylene class of antiestrogens are predominantly agonists for the induction of these genes in the uterus.

IT **68047-06-3**, 4-Hydroxy-tamoxifen
RL: ADV (Adverse effect, including toxicity); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(triphenylethylene antiestrogens induce uterine vascular **endothelial** growth factor expression via partial estrogen agonist activity)

IT **10540-29-1**, Tamoxifen
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(triphenylethylene antiestrogens induce uterine vascular **endothelial** growth factor expression via partial estrogen agonist activity)

L9 ANSWER 21 OF 52 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:520892 HCAPLUS
DOCUMENT NUMBER: 127:185944

TITLE: Estrogen acutely stimulates nitric oxide synthase activity in fetal pulmonary artery endothelium

AUTHOR(S): Lantin-Hermoso, Regina L.; Rosenfeld, Charles R.; Yuhanna, Ivan S.; German, Zohre; Chen, Zhong; Shaul, Philip W.
CORPORATE SOURCE: Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX, 75235, USA

SOURCE: Am. J. Physiol. (1997), 273(1, Pt. 1), L119-L126
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Estrogen (E) has nitric oxide (NO)-mediated effects in certain vascular beds, and fetal E levels rise acutely with parturition, suggesting that E may be involved in NO-mediated pulmonary vasodilation at birth. We tested the hypothesis that E acutely stimulates NO synthase (NOS) activity in ovine fetal pulmonary artery endothelial cells (PAEC) by measuring L-[3H]arginine conversion to L-[3H]citrulline in intact cells. NOS activity in the presence of 17.beta.-estradiol (E2.beta.) rose in a dose-dependent manner, increasing 70-100%, with a threshold concn. of 10-10 M. This effect was detectable within 5 min of E2.beta. exposure, and the maximal response was comparable to that obtained with acetylcholine, which had a threshold concn. of 10-8 M. Ca2+ removal completely inhibited E2.beta.-stimulated NOS activity, and activity with E2.beta. and the Ca2+ ionophore A-23187 was not additive. In addn., the expression of the endothelial isoform of NOS (eNOS) was not altered, and

the inducible and neuronal NOS isoforms were not detected by immunoblot anal. These findings indicate that E2.beta. acutely stimulates eNOS by Ca2+ influx. Furthermore, E2.beta.-stimulated NOS activity was fully inhibited by the E receptor (ER) antagonists tamoxifen and ICI-182,780, and ER mRNA expression was evident in reverse transcription-polymerase chain reaction assays. Thus, E acutely stimulates eNOS activity in fetal PAEC via the activation of endothelial ER and increases in intracellular Ca2+.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(estrogen stimulation of nitric oxide synthase in fetal pulmonary artery **endothelium**)

L9 ANSWER 22 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:440538 HCAPLUS
DOCUMENT NUMBER: 127:131167
TITLE: Estrogen relaxation of coronary artery smooth muscle is mediated by nitric oxide and cGMP
AUTHOR(S): Darkow, David J.; Lu, Luo; White, Richard E.
CORPORATE SOURCE: Dep. Physiology and Biiophysics, Wright State Univ. Sch. Medicine, Dayton, OH, 45435, USA
SOURCE: Am. J. Physiol. (1997), 272(6, Pt. 2), H2765-H2773
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Estrogens are proposed to exert protection against cardiovascular disease, and evidence now suggests that this protection involves a direct vasodilatory effect. We have shown previously that estrogen relaxes endothelium-denuded porcine coronary arteries by opening the large-conductance calcium- and voltage-activated potassium (BKCa) channel of myocytes through cGMP-dependent phosphorylation. The present study confirms these results and now demonstrates that this mechanism involves prodn. of nitric oxide (NO). S-nitroso-N-acetylpenicillamine (SNAP), an NO donor, or 8-bromo-cGMP mimicked the effect of estrogen on BKCa channels. Furthermore inhibition of NO synthase (NOS) attenuated estrogen- or tamoxifen-induced BKCa-channel activity, and this effect was disinhibited by L-arginine. Inhibition of guanyl cyclase activity blocked the stimulatory effect of estrogen, SNAP, or L-arginine on BKCa channels. Furthermore, 17.beta.-estradiol stimulated accumulation of nitrite and cGMP in coronary myocytes. Therefore, we propose that the vasodilatory effect of estrogen on the coronary circulation is mediated by NO. A portion of the beneficial cardiovascular effects of estrogen may be attributed to relaxation of vascular smooth muscle by a process that involves NO- and cGMP-dependent stimulation of BKCa channels.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(estrogen relaxation of coronary artery smooth **muscle** mediation by nitric oxide and cGMP)

L9 ANSWER 23 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:177501 HCAPLUS
DOCUMENT NUMBER: 126:262253
TITLE: Hypotonicity-induced changes in anion permeability of cultured rat brain endothelial cells
AUTHOR(S): von Weikersthal, Sophia F.; Hickman, Margaret E.; Hladky, Stephen B.; Barrand, Margery A.
CORPORATE SOURCE: Department of Pharmacology, University of Cambridge, Tennis Court Road, Cambridge, CB2 1QJ, UK
SOURCE: Biochim. Biophys. Acta (1997), 1325(1), 99-107
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Iodide efflux, an index of anion permeability, has been monitored in cultured rat brain endothelial cells. Following hypotonicity-induced swelling, large, rapid increases in permeability occur, the extent of these increases depending on the degree of hypotonicity. Such large responses are not obsd. with rat aortic endothelial cells. Results of anion substitution expts. suggest that iodide efflux is via a chloride channel rather than an exchanger. The efflux increase is blocked by NPPB (100 .mu.M) but not by DIDS or DPC at 100 .mu.M. It is dependent on intracellular ATP but unaffected by removal of external calcium. Increasing internal calcium using A23187 does not produce a change in efflux, but depletion of calcium reduces or eliminates the response to hypotonicity. The response is reduced by pimozide (2-50 .mu.M) that inhibits the actions of calmodulin and by pBPB (10 .mu.M) that affects phospholipase A2 activity. It is eliminated by 5-lipoxygenase inhibitors (L-656,224 and ETH615, 10 .mu.M) but is unaffected by cyclo-oxygenase inhibitors (indomethacin and piroxicam, 1-100 .mu.M). It is blocked by some modulators of P-glycoprotein activity, e.g., verapamil (100 .mu.M), tamoxifen (50 .mu.M), and progesterone (100 .mu.M) but not by others, e,g., forskolin (40 .mu.M), dideoxyforskolin (40 .mu.M), quinidine (100 .mu.M) and cyclosporin A (10 .mu.M).

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(effect on hypotonicity-induced changes in anion permeability of cultured rat brain **endothelial** cells)

L9 ANSWER 24 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:85571 HCAPLUS
DOCUMENT NUMBER: 126:156430
TITLE: Method for identifying an agent which increases TGF-beta levels
INVENTOR(S): Grainger, David J.; Metcalfe, James C.
PATENT ASSIGNEE(S): Neorx Corporation, USA
SOURCE: U.S., 39 pp. Cont.-in-part of U.S. Ser. No. 242,161, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5595722	A	19970121	US 1995-476735	19950607
US 5847007	A	19981208	US 1994-242161	19940512
US 5599844	A	19970204	US 1995-528810	19950915
US 5773479	A	19980630	US 1995-560808	19951121
CA 2223595	AA	19961219	CA 1996-2223595	19960607
WO 9640098	A2	19961219	WO 1996-US10211	19960607
WO 9640098	A3	19970619		
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
AU 9662773	A1	19961230	AU 1996-62773	19960607
EP 833624	A2	19980408	EP 1996-921577	19960607
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 11510479	T2	19990914	JP 1996-502239	19960607
US 5733925	A	19980331	US 1996-738733	19961028
US 5945456	A	19990831	US 1997-965254	19971106
US 6197789	B1	20010306	US 1997-973570	19971205

PRIORITY APPLN. INFO.: US 1993-11669 B2 19930128
US 1993-61714 B2 19930513

US 1993-62451	B2	19930513
US 1994-241844	A2	19940512
US 1994-242161	A2	19940512
US 1994-300357	A1	19940902
US 1995-450793	A3	19950525
US 1995-476735	A	19950607
US 1995-477393	A	19950607
US 1995-478936	A	19950607
US 1995-486334	A	19950607
US 1995-560808	A1	19951121
WO 1996-US10211	W	19960607

OTHER SOURCE(S): MARPAT 126:156430

AB A method for identifying a compd. that is a TGF-beta activator or prodn. stimulator is provided. The method uses human aortic smooth muscle cells (hVSMC) and monoclonal or polyclonal anti-.beta.-TGF antibody and det. the rate of proliferation of hVSMC or prodn. of TGF-.beta. mRNA in hVSMC. The TGF-.beta. activator is useful for preventing or treating cardiovascular indication characterized by decreased lumen diam., e.g. atherosclerosis, thrombosis, myocardial infarction and stroke.

IT **10540-29-1**, Tamoxifen
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(human aortic smooth **muscle** cells and mono- or poly-clonal anti-.beta.-TGF antibody for screening TGF-.beta. activator useful for treating cardiovascular diseases)

L9 ANSWER 25 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:472476 HCAPLUS
DOCUMENT NUMBER: 125:133134
TITLE: Antiestrogens inhibit endothelial cell growth stimulated by angiogenic growth factors
AUTHOR(S): Gagliardi, Antonio R.; Hennig, Bernhard; Collins, Delwood C.
CORPORATE SOURCE: Medical Research Service, University Kentucky, Lexington, KY, USA
SOURCE: Anticancer Res. (1996), 16(3A), 1101-1106
CODEN: ANTRD4; ISSN: 0250-7005
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have previously reported that the partial estrogen antagonists, tamoxifen, clomiphene and nafoxidine, inhibited angiogenesis in vivo in a dose-related manner in the six-day old chick egg chorioallantoic membrane (CAM) assay. In the present study, the authors investigated the effect of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) on the growth of porcine pulmonary artery and human dermal microvascular endothelial cells. Both of these growth factors significantly increased the growth of these cells. The antiproliferative activity of the partial antiestrogens, tamoxifen, nafoxidine and clomiphene, and the pure antiestrogen, ICI 182,780, was detd. Tamoxifen, clomiphene, nafoxidine and ICI 182,780 significantly inhibited endothelial cell growth stimulated by bFGF and VEGF. This inhibition of endothelial cells was not altered by the presence of up to 30 .mu.M of estradiol-17.beta.. These results indicate that the anti-angiogenic action of the antiestrogens does not occur via the estrogen receptor, but by a direct inhibition of growth factor stimulated endothelial cell growth.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(antiestrogens inhibit **endothelial** cell growth stimulated by angiogenic growth factors)

L9 ANSWER 26 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:375666 HCAPLUS
DOCUMENT NUMBER: 125:75792
TITLE: Tamoxifen (estrogen antagonist) inhibits voltage-gated

calcium current and contractility in vascular smooth muscle from rats
AUTHOR(S): Song, Jianben; Standley, Paul R.; Zhang, Feng; Joshi, Darius; Gappy, Saib; Sowers, James R.; Ram, Jeffrey L.
CORPORATE SOURCE: Dep. Physiol., Wayne State Univ., Detroit, MI, USA
SOURCE: J. Pharmacol. Exp. Ther. (1996), 277(3), 1444-1453
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tamoxifen (Tx) has been used in breast cancer treatment and prophylaxis because of its antiestrogenic activity; however, Tx may also have beneficial cardiovascular effects and other actions mediated by mechanisms other than estrogen receptors. Previous studies showing interactions of Tx with Ca++-channel blockers suggested that Tx may affect Ca++ channels, an hypothesis that was investigated using whole cell patch clamp techniques in vascular smooth muscle cells (cell line A7r5 and freshly dissocd. cells) and by detg. effects on contractions of isolated blood vessels. Tx reduced current through L-type Ca++ channels, with an ID50 of 2 .times. 10-6 M when applied by cumulative addn. to A7r5 cells. With acute application, 10-6 M Tx significantly reduced L-type current in A7r5 cells within 2 min to 88% of control (vehicle, 0.1% ethanol) in A7r5 cells, 67% of control in aortic vascular smooth muscle cells, and 60% of control in tail artery vascular smooth muscle cells. Tx also decreased the rate of inactivation of L-type current. Inhibition of T-type current by Tx was less than for L-type current but was significant at 10-5 M Tx. Treatment of tail artery rings with Tx (10-5 M, 15 min; 10-6 M, 4 h) reduced K+-elicited contractions. Since therapeutic concns. of Tx during treatment may exceed 10-6 M, these effects of Tx on vascular smooth muscle Ca++ channels and vessel contractions may have a role in the efficacy and side-effects of Tx treatment.
IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tamoxifen inhibits voltage-gated calcium current and contractility in vascular smooth **muscle**)

L9 ANSWER 27 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:234315 HCAPLUS
DOCUMENT NUMBER: 124:279469
TITLE: 17.beta.-Estradiol and smooth muscle cell proliferation in aortic cells of male and female rats
AUTHOR(S): Espinosa, Emma; Oemar, Barry S.; Luescher, Thomas F.
CORPORATE SOURCE: Cardiovascular Res., Univ. Hosp., Bern, CH-3010, Switz.
SOURCE: Biochem. Biophys. Res. Commun. (1996), 221(1), 8-14
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The low incidence of cardiovascular disease in women before menopause or during hormone replacement therapy suggests a protective effect of estrogens. The mechanism(s) are uncertain but may involve effects on lipids, coagulation and the endothelium. Vascular smooth muscle cell (VSMC) proliferation also contributes to atherosclerosis. Hence, we investigated whether 17.beta.-estradiol (E2) inhibits VSMC proliferation. VSMC of 6 female and 6 male Wistar Kyoto rats (WKY; age 10-12 wk) were incubated for 24 h with E2 and/or fetal calf serum (FCS). E2 (10-9-10-5 M) alone reduced [3H]thymidine uptake at 10-5 M in female cells only. In female and male VSMC, FCS (1%) increased [3H]thymidine uptake (4.5-fold). When given simultaneously, E2 did not prevent this effect of FCS (1%). However, when cells were preincubated for 24 h with E2 and then stimulated with FCS, [3H]thymidine uptake was reduced by E2 at 10-5 M in female VSMC, while in male VSMC this effect was minimal. Both female and male VSMC expressed estrogen receptors as demonstrated by RT-PCR. Pretreatment of female VSMC cells with the E2 receptor antagonist tamoxifen prevented the antiproliferative effects exerted by E2. In aortic VSMC of female rats, E2 moderately inhibited proliferation on its own and during stimulation

with FCS, while this effect was small in VSMC of male rats. The expression of the E2 receptor in female and male VSMC and the effects of tamoxifen suggest that this effect is mediated by E2 receptors.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(estradiol effects on aorta smooth **muscle** cell proliferation in male and female rats)

L9 ANSWER 28 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:120873 HCAPLUS
DOCUMENT NUMBER: 124:219658
TITLE: Blockers of volume-activated Cl- currents inhibit endothelial cell proliferation
AUTHOR(S): Voets, Thomas; Szucs, Geza; Droogmans, Guy; Nilius, Bernd
CORPORATE SOURCE: Lab. voor Fysiologie, KU Leuven, Louvain, B-3000, Belg.
SOURCE: Pfluegers Arch. (1995), 431(1), 132-4
CODEN: PFLABK; ISSN: 0031-6768
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Vol.-activated Cl- currents (ICl,vol) and cell growth have been measured in cultured endothelial cells from bovine pulmonary artery (CPAE) in the absence and presence of compds. which block these currents. The anti-estrogen drug tamoxifen, which efficiently arrests the growth of breast cancer cells (1), inhibits both ICl,vol and cell proliferation with IC50 of 3.8 and 4.8 .mu.mol/l resp. NPPB and quinine, which also block ICl,vol, inhibit the growth of CPAE cells as well. Current and cell growth were closely correlated under all these conditions. We conclude that ICl,vol might be involved in the control of endothelial cell growth and thus might be important for the modulation of vascularization and vascular remodelling.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blockers of vol.-activated Cl- currents inhibit **endothelial** cell proliferation)

L9 ANSWER 29 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:59311 HCAPLUS
DOCUMENT NUMBER: 124:106793
TITLE: Effects of sex hormones on oncogene expression in the vagina and on development of sexual dimorphism of the pelvis and anococcygeus muscle in the mouse
AUTHOR(S): Iguchi, Taisen; Fukazawa, Yugo; Bern, Howard A.
CORPORATE SOURCE: Department Biology, Yokohama City University, Yokohama, 236, Japan
SOURCE: Environ. Health Perspect. Suppl. (1995), 103(Suppl. 7), 79-82
CODEN: EHPSEO; ISSN: 1078-0475
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 34 refs., of genital and nongenital abnormalities found in mice exposed neonatally to the estrogen DES and to the antiestrogen tamoxifen. Topics discussed were: proto-oncogene expression in vagina and uterus of mice exposed neonatally to DES; mouse pelvis in relation to sexual dimorphism and responsiveness to steroid hormones; and mouse anococcygeus muscle in relation to sexual dimorphism and responsiveness to steroid hormones.

IT **10540-29-1**, Tamoxifen
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(sex hormones effect on oncogene expression in the vagina and on development of sexual dimorphism of pelvis and anococcygeus **muscle**)

L9 ANSWER 30 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:647512 HCAPLUS
DOCUMENT NUMBER: 123:73974
TITLE: Muscle damage revisited: does tamoxifen protect by membrane stabilization or radical scavenging, rather than via the E2-receptor?
AUTHOR(S): Bar, P. Dop R.; Koot, Radboud W.; Amelink, G. Hans J.
CORPORATE SOURCE: Dep. Neurology, Utrecht Univ. Hospital, Utrecht, 3584 CX, Neth.
SOURCE: Biochem. Soc. Trans. (1995), 23(2), 236S
CODEN: BCSTB5; ISSN: 0300-5127
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 8 refs.
IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(does tamoxifen protect **muscles** by membrane stabilization or radical scavenging, rather than via E2-receptor)

L9 ANSWER 31 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:444167 HCAPLUS
DOCUMENT NUMBER: 122:205191
TITLE: Prevention and treatment of pathologies associated with abnormally proliferative smooth muscle cells with TGF-.beta. activators
INVENTOR(S): Grainger, David J.; Metcalfe, James C.; Weissberg, Peter L.
PATENT ASSIGNEE(S): NeorX Corp., USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9426303	A1	19941124	WO 1994-US5265	19940512
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2162586	AA	19941124	CA 1994-2162586	19940512
EP 710116	A1	19960508	EP 1994-917956	19940512
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08510451	T2	19961105	JP 1994-525687	19940512
US 5472985	A	19951205	US 1994-300357	19940902
US 5599844	A	19970204	US 1995-528810	19950915
US 5773479	A	19980630	US 1995-560808	19951121
US 5945456	A	19990831	US 1997-965254	19971106

PRIORITY APPLN. INFO.:
US 1993-61714 A 19930513
WO 1994-US5265 W 19940512
US 1994-300357 A1 19940902
US 1995-560808 A1 19951121

AB TGF-.beta. activators and TGF-.beta. prodn. stimulators are employed to maintain or increase vessel lumen diam. in a diseased or injured vessel of a mammal. Conditions such as restenosis following angioplasty, vascular bypass grafts, transplanted organs, atherosclerosis, or hypertension are characterized by a reduced vessel lumen diam. In a preferred embodiment of the invention, TGF-.beta. activators and prodn. stimulators inhibit abnormal proliferation of smooth muscle cells. TGF-.beta. activators or prodn. stimulators that are not characterized by an undesirable systemic toxicity profile at a prophylactic dose are also amenable to chronic use for prophylactic purposes with respect to disease states involving proliferation and/or migration of vascular smooth muscle cells over time. Further provided is a method for detg. TGF-.beta. in vitro, thereby

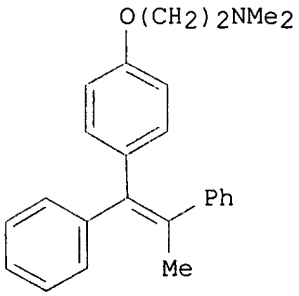
identifying a patient at risk for atherosclerosis and monitoring a recipient that has received one or more administrations of a TGF-.beta. activator or prodn. stimulator. Effects of tamoxifen and heparin on the proliferation of cultured vascular muscle cells and effects of inhibition of TGF-.beta. activation in transgenic apo(o) ice were also demonstrated.

IT **10540-29-1**, Tamoxifen **13002-65-8**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention and treatment of pathologies assocd. with abnormally proliferative smooth **muscle** cells with TGF-.beta. activators)

L9 ANSWER 32 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:383012 HCAPLUS
DOCUMENT NUMBER: 122:151384
TITLE: Methods for inhibiting aortal smooth muscle cell proliferation and restenosis with 1,1,2-triphenylbut-1-ene derivatives
INVENTOR(S): Fontana, Steven A.
PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA
SOURCE: U.S., 5 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5384332	A	19950124	US 1994-241240	19940511
CA 2149092	AA	19951112	CA 1995-2149092	19950510
EP 681836	A1	19951115	EP 1995-303139	19950510
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 07304660	A2	19951121	JP 1995-111817	19950510

PRIORITY APPLN. INFO.: US 1994-241240 19940511
GI



I

AB Methods for inhibiting aortal smooth muscle cell proliferation, particularly restenosis, in humans, comprise administering an effective amt. of I (when R1 = R2, R1, R2 = Me, Et; when R1 .noteq. R2, 1 of R1, R2 = Me, Et and the other of R1, R2 is benzyl), or a pharmaceutically acceptable salt thereof. Using a postmenopausal model to det. the effects of different treatments on test animal uteri, activity indicates that the compds. of the invention have potential in the treatment of aortal smooth muscle cell proliferation, esp. restenosis. Formulations contg. an active ingredient of the invention are presented.

IT **161400-98-2 161400-99-3 161401-00-9 161401-01-0 161401-02-1**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(triphenylbutene derivs. for inhibition of aortal smooth **muscle**

cell proliferation and restenosis)

L9 ANSWER 33 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:340981 HCAPLUS
DOCUMENT NUMBER: 122:96515
TITLE: Therapeutic inhibitor of vascular smooth muscle cells
INVENTOR(S): Kunz, Lawrence Leroy; Klein, Richard A.; Reno, John M.; Grainger, David J.; Metcalfe, James C.; Weissberg, Peter L.; Anderson, Peter G.
PATENT ASSIGNEE(S): Neorx Corp., USA
SOURCE: PCT Int. Appl.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9426291	A1	19941124	WO 1994-US5266	19940512
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2162587	AA	19941124	CA 1994-2162587	19940512
EP 702557	A1	19960327	EP 1994-916743	19940512
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08510209	T2	19961029	JP 1994-523613	19940512
US 5733925	A	19980331	US 1996-738733	19961028

PRIORITY APPLN. INFO.:
US 1993-62451 A 19930513
US 1993-11669 B2 19930128
WO 1994-US5266 W 19940512
US 1995-450793 A3 19950525

AB Sustained release dosage forms of TGF-beta activators and TGF-beta prodn. stimulators are employed to maintain or increase vessel lumen diam. in a diseased or injured vessel of a mammal. Conditions such as restenosis following angioplasty, vascular bypass grafts, transplanted organs, atherosclerosis or hypertension are characterized by a reduced vessel lumen diam. In a preferred embodiment of the invention, TGF-beta activators and prodn. stimulators inhibit abnormal proliferation of smooth muscle cells. Free TGF-beta activators or prodn. stimulators that are not characterized by an undesirable systemic toxicity profile at a prophylactic dose may be used in conjunction with the sustained release dosage forms described herein for prophylactic purposes with respect to disease and trauma states involving proliferation and/or migration of vascular smooth muscle cells over time.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TGF-beta activators and prodn. stimulators as therapeutic inhibitors of vascular smooth **muscle** cells)

L9 ANSWER 34 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:196201 HCAPLUS
DOCUMENT NUMBER: 122:513
TITLE: Tamoxifen enhances cell death in implanted MCF7 breast cancer by inhibiting endothelium growth
AUTHOR(S): Haran, E. Furman; Maretzek, A. F.; Goldberg, I.; Horowitz, A.; Degani, H.
CORPORATE SOURCE: Chem. Phys. Dep., Weizmann Inst. Sci., Rehovot, 76100, Israel
SOURCE: Cancer Res. (1994), 54(21), 5511-14
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Magnetic resonance imaging at high spatial resoln. and histochem. staining were applied to monitor the influence of tamoxifen vs. estrogen on the growth, endothelial d., and extent of necrosis in tumors of MCF7 human

breast cancer cells implanted in nude mice. Concomitantly with tamoxifen growth arrest, a highly significant decrease, by more than 2-fold, in the endothelial d. of viable tumor regions had occurred, together with a significant increase in the extent of necrosis. The results suggest that the antiestrogenic activity of tamoxifen in breast cancer, which results in enhanced necrosis and tumor regression, is due to the inhibition of angiogenesis and endothelial growth, thus reducing vascularization and impairing tumor perfusion.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tamoxifen enhancement of breast cancer cell death by inhibition of angiogenesis and **endothelium** growth)

L9 ANSWER 35 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:575851 HCAPLUS
DOCUMENT NUMBER: 121:175851
TITLE: Permeation properties and modulation of volume-activated Cl--currents in human endothelial cells
AUTHOR(S): Nilius, Bernd; Sehrer, Jan; Droogmans, Guy
CORPORATE SOURCE: Laboratorium voor Fysiologie, K. U. Leuven, Louvain, B-3000, Belg.
SOURCE: Br. J. Pharmacol. (1994), 112(4), 1049-56
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have studied the permeation and pharmacol. properties of a recently described vol.-activated, calcium-insensitive, small-conductance Cl--channel in endothelial cells from human umbilical vein. The relative permeability for various anions was I->Cl-.apprx.Br->F->gluconate- (1.63 .+-. 0.36:1:0.95 .+-. 0.16:0.46 .+-. 0.04:0.19 .+-. 0.07, n = 10). 5-Nitro-2-(3-phenylpropylamino)-benzoic acid (NPPB) induced a fast and reversible block of the current (K1 = 29 .mu.mol L-1). Extracellular ATP induced a low-affinity block of the current, that showed a small voltage-dependence (K1 = 4.9 mmol L-1 at +80 mV and K1 = 8.2 mmol L-1 at -80 mV). Extracellularly applied arachidonic acid (10 .mu.mol L-1) irreversibly blocked the current in 5 out of 9 cells. This block seems to be non-specific, because other ionic currents, e.g. inwardly rectifying K+ currents, were blocked as well. Tamoxifen induced a high affinity block of the current (K1 = 2.9 .mu.mol L-1). Block and reversal of block were however much slower than with NPPB. Cytotoxic compds., which are substrates of the P-glycoprotein multidrug transporter, loaded into endothelial cells via the patch pipet, exerted only minor effects on the vol.-activated current. Vinblastine and colcemid did not affect the vol.-activated current, whereas daunomycin and vincristine induced a slow 'run-down' of the current. The similarity between permeation and pharmacol. properties of vol.-activated Cl--currents in endothelial cells and those in many other cell types may suggest that they all belong to the same family of vol.-activated small-conductance Cl--channels. Evidence that they belong to the class of P-glycoprotein assocd. Cl--channels is however only marginal, whereas their biophys. characteristics differ significantly from those of the ClC-2 vol.-activated Cl--channels.

IT **10540-29-1**, Tamoxifen
RL: BIOL (Biological study)
(chloride current of human vein **endothelial** cells blockage by)

L9 ANSWER 36 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:125245 HCAPLUS
DOCUMENT NUMBER: 120:125245
TITLE: Titration of the in vivo uptake of 16.alpha.-[18F]fluoroestradiol by target tissues in the rat: competition by tamoxifen, and implications for quantitating estrogen receptors in vivo and the use of animal models for receptor-binding

radiopharmaceutical development
AUTHOR(S): Katzenellenbogen, John A.; Mathias, Carla J.; Vanbrocklin, Henry F.; Brodack, James W.; Welch, Michael J.
CORPORATE SOURCE: Dep. Chem., Univ. Illinois, Urbana, IL, 61801, USA
SOURCE: Nucl. Med. Biol. (1993), 20(6), 735-45
CODEN: NMBIEO; ISSN: 0883-2897
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have measured in vivo the uptake of 16.alpha.-[18F]estradiol (FES) by target tissues in the immature rat at increasing dose levels (obtained by diln. of [18F]FES with unlabeled estradiol). This was done to examine the binding capacity of target tissues in vivo and to det. whether the uptake in receptor-rich tissues was flow limited, as this has implications concerning the appropriateness of using receptor-rich tissues in exptl. animals as models for FES uptake by receptor-poor breast tumors in humans. The authors also wanted to establish the dose level of the anti-estrogen tamoxifen required to block target tissue uptake of FES. The authors found that in untreated rats, specific uptake in the uterus satd. at c. 180 pmol/g, in the ovary at c. 54 pmol/g and in the muscle at c. 2 pmol/g. At an intermediate dose of tamoxifen (570 .mu.g/kg), uptake satd. at somewhat lower levels, and at a high tamoxifen dose (1710 .mu.g/kg), yet lower specific uptake was evident. In the FES titrns. at low dose levels of FES, both the uterus and the ovaries, but not the muscle, showed characteristics of flow-limited uptake, i.e. the uptake-to-dose ratio reached a max. level. This flow limitation suggests that only when receptor levels are sufficiently low will the FES uptake be related to receptor concn. While receptor-rich tissues such as the rat uterus will show this flow limitation, the receptor concn. in most primary and metastatic human breast tumors is sufficiently low, so that the uptake should parallel receptor content. In in vivo distribution studies, target tissues (or tumors) with low receptor content will be more fully satd. and ligand more readily displaced. Also, uptake by secondary target tissues (i.e. those with a lower content of estrogen receptor, such as muscle, thymus and kidney) may be better models for assessing the effectiveness of new breast tumor imaging agents than uptake by receptor-rich tissues.

IT **10540-29-1**, Tamoxifen
RL: BIOL (Biological study)
(fluoroestradiol uptake block by, estrogen receptor concn. in relation to, in **muscle** and ovary and uterus)

L9 ANSWER 37 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:531107 HCAPLUS
DOCUMENT NUMBER: 119:131107
TITLE: Tamoxifen decreases the rate of proliferation of rat vascular smooth-muscle cells in culture by inducing production of transforming growth factor .beta.
AUTHOR(S): Grainger, David J.; Weissberg, Peter L.; Metcalfe, James C.
CORPORATE SOURCE: Dep. Biochem., Univ. Cambridge, Cambridge, CB2 1QW, UK
SOURCE: Biochem. J. (1993), 294(1), 109-12
CODEN: BIJOAK; ISSN: 0306-3275
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tamoxifen selectivity and reversibly decreased the rate of proliferation of adult rat aortic vascular smooth-muscle cells (VSMCs). Half-maximal inhibition of proliferation occurred at 2-5 .mu.M tamoxifen for VSMCs and at >50 .mu.M for adventitial fibroblasts. The cell cycle time for all the VSMCs in the population was increased from 35 .+-. 2 h to 54 .+-. 4 h in the presence of 33 .mu.M tamoxifen. Tamoxifen did not affect the time of entry into DNA synthesis, but delayed arrival at mitosis by >24 h. It therefore extended the duration of the G2-to-M phase of the cell cycle. However, the rate of proliferation of VSMCs was not decreased by tamoxifen (at concns. at to 50 .mu.M) in the presence of neutralizing antibody to transforming growth factor .beta. (TGF-.beta.). The level of mRNA for TGF-.beta.1 in VSMCs was strongly induced by 10 .mu.M tamoxifen, and

TGF-.beta. activity in conditioned medium from tamoxifen-treated cells was more than 50-fold higher than from control cells. Tamoxifen therefore extended the G2-to-M phase of the cell cycle in VSMCs by increasing TGF-.beta. activity in the culture.

IT **10540-29-1**, Tamoxifen
RL: BIOL (Biological study)
(vascular smooth **muscle** cell proliferation inhibition by, transforming growth factor .beta. induction in relation to)

L9 ANSWER 38 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:34763 HCAPLUS
DOCUMENT NUMBER: 116:34763
TITLE: Tamoxifen and estrogen both protect the rat muscle against physiological damage
AUTHOR(S): Koot, R. W.; Amelink, G. J.; Blankstein, M. A.; Bar, P. R.
CORPORATE SOURCE: Dep. Neurol., Univ. Utrecht, Utrecht, Neth.
SOURCE: J. Steroid Biochem. Mol. Biol. (1991), 40(4-6), 689-95
CODEN: JSBBEZ; ISSN: 0960-0760
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tamoxifen (TX), an estrogen antagonist, was used to characterize the protective effect of estradiol (E2) on exercise-related creatine kinase (CK) release from skeletal muscle of the rat. S.c. administration of TX for 3 wk in female rats had a profound antiestrogen effect as evidenced by a reduced wt. of the uterus. The CK release after elec. stimulation of the isolated soleus muscle, previously shown to be E2-dependent, was markedly reduced (30-50%) after treatment with TX; this observation points to an E2-like protective action of TX instead of E2-antagonism. This effect was dose-dependent (0.25-1.00 mg/kg) and was not seen when TX was given shortly (24 h) before the expts. In ovariectomized females, that show more CK leakage due to the lack of circulating E2, both E2- and TX-treatment resulted in a 60% redn. of the CK leakage. Muscles from male rats, treated with TX, showed a similar response: after contractions the CK release was significantly lower. Thus, TX, like E2, reduces contraction-induced muscle damage in the rat and, thus, has E2-agonistic properties on skeletal rat muscle.

IT **10540-29-1**, Tamoxifen
RL: BIOL (Biological study)
(exercise-induced **muscle** damage prevention by)

L9 ANSWER 39 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:549907 HCAPLUS
DOCUMENT NUMBER: 115:149907
TITLE: The combination of a bacterial polysaccharide and tamoxifen inhibits angiogenesis and tumor growth
AUTHOR(S): Tanaka, N. G.; Sakamoto, N.; Korenaga, H.; Inoue, K.; Ogawa, H.; Osada, Y.
CORPORATE SOURCE: Res. Inst., Daiichi Pharm. Co., Ltd., Tokyo, 134, Japan
SOURCE: Int. J. Radiat. Biol. (1991), 60(1-2), 79-83
CODEN: IJRBE7; ISSN: 0955-3002
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The synergistic antiangiogenic effects of SP-PG, a bacterial polysaccharide isolated from Arthrobacter sp., with antiestrogens widely used for breast cancer patients were demonstrated. The combination of SP-PG and the antiestrogen tamoxifen (TAM), is effective in inhibiting tumor growth. This effectiveness was not dependent on the estrogen receptor or TAM sensitivity of the tumor cells. The antitumor effects of the combination are considered to be due to their synergistic antiangiogenic activities mediated by antiproliferative effects on endothelial cells.

IT **54965-24-1**, Tamoxifen citrate
RL: BIOL (Biological study)
(polysaccharide of Arthrobacter sp. synergistic antiangiogenic effect

with, inhibition of **endothelial** cell proliferation in, antitumor activity against human breast cancer cells in relation to)

L9 ANSWER 40 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1988:31649 HCAPLUS
DOCUMENT NUMBER: 108:31649
TITLE: The antiestrogen tamoxifen is a calcium antagonist in perfused rat mesentery
AUTHOR(S): Lipton, A.
CORPORATE SOURCE: Efamol Res. Inst., NS, B4N 4H8, Can.
SOURCE: Cancer Chemother. Pharmacol. (1987), 20(2), 125-7
CODEN: CCPHDZ; ISSN: 0344-5704
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The antiestrogen tamoxifen at 10-7-10-5 M induced concn.-related inhibition of K+-stimulated vasospasm in the isolated perfused rat mesentery vascular bed. In contrast, responses to noradrenaline did not fall below control levels until the tamoxifen concn. exceeded 4 .times. 10-6 M. Recovery of the K+-stimulated responses was also concn. related. The most likely explanation is that while tamoxifen can obstruct the entry of extracellular Ca, it is unable to prevent the intracellular release of the ion by noradrenaline.
IT **10540-29-1**, Tamoxifen
RL: BIOL (Biological study)
(as calcium antagonist, mesenteric artery **muscle** contraction inhibition by)

L9 ANSWER 41 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:78991 HCAPLUS
DOCUMENT NUMBER: 106:78991
TITLE: Calcium antagonism by the antiestrogen tamoxifen
AUTHOR(S): Lipton, A.; Morris, I. D.
CORPORATE SOURCE: Med. Sch., Univ. Manchester, Manchester, M13 9PT, UK
SOURCE: Cancer Chemother. Pharmacol. (1986), 18(1), 17-20
CODEN: CCPHDZ; ISSN: 0344-5704
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tamoxifen [**10540-29-1**] (10-6, or 10-5M) in vitro inhibited the contraction of smooth **muscle** from rat myometrium and aorta produced by exogenous Ca. At the same concn. tamoxifen did not affect the uptake of Ca into the **muscle**. The importance of Ca in cell proliferation suggests that some of the unexplained antitumor activity of the estrogen antagonists may be accounted for by intracellular Ca antagonism.

L9 ANSWER 42 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:571644 HCAPLUS
DOCUMENT NUMBER: 103:171644
TITLE: Evidence that tamoxifen is a histamine antagonist
AUTHOR(S): Kroeger, Edwin A.; Brandes, Lorne J.
CORPORATE SOURCE: Dep. Physiol., Univ. Manitoba, Winnipeg, MB, R3E 0V9, Can.
SOURCE: Biochem. Biophys. Res. Commun. (1985), 131(2), 750-5
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tamoxifen [**10540-29-1**], N,N-diethyl-2-[(4-phenylmethyl)phenoxy]ethanamine (DPPE) [98774-23-3], and established histaminic H1-antagonists specifically block the histamine [51-45-6]-induced (H1) contraction of canine tracheal smooth **muscle** in the order: pyrilamine [91-84-9] = hydroxyzine [68-88-2] > tamoxifen = 4-hydroxytamoxifen [**68047-06-3**] > DPPE. The H1-antagonist hydroxyzine, which competes about equally with DPPE for the antiestrogen binding site, is up to 103-fold stronger than DPPE in blocking histamine-induced **muscle** contraction. Thus, H1 antagonism is distinct from binding to the antiestrogen binding site and

if the latter is a histamine receptor, it is not H1; presumably tamoxifen and DPPE compete for this novel site in addn. to, and with greater affinity than, the H1 receptor.

L9 ANSWER 43 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:481386 HCAPLUS
DOCUMENT NUMBER: 103:81386
TITLE: Inhibition of intestinal smooth muscle function by tamoxifen and clomiphene
AUTHOR(S): Morris, Ian D.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Manchester, Manchester, M13 9PT, UK
SOURCE: Life Sci. (1985), 37(3), 273-8
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The acute in vitro effects of the estrogen antagonists clomiphene [911-45-5] and tamoxifen [**10540-29-1**] were examd. on spasmogen-induced contractions of the guinea pig ileum. Both estrogen antagonists inhibited the contractions produced by acetylcholine [51-84-3], the muscarinic agonist .beta.-methylcholine [7562-87-0], histamine [51-45-6], and bradykinin [58-82-2], in a manner which suggests noncompetitive antagonism. Concn.-effect curves to each of the spasmogens were unaffected using 0.1 .mu.M of either of the estrogen antagonists. Clomiphene at 1 .mu.M reduced the max. response to the spasmogens by 20%-50%. Tamoxifen, at the same concn., also inhibited the contractions but to a much smaller extent. Clomiphene at the highest concn. tested, 10 .mu.M, completely suppressed contractions to all the spasmogens. Tamoxifen, at 10 .mu.M, completely suppressed contractions to .beta.-methylcholine and bradykinin. A residual response to acetylcholine and histamine remained, and this was abolished by raising the concn. to 100 .mu.M. Clomiphene was apparently more potent than tamoxifen on the inhibition of the contractions of the ileum. The results demonstrate a nonspecific effect of the estrogen antagonists on smooth **muscle** function and do not substantiate early reports of specific anticholinergic activity. The possibility of these effects contributing to both the side effects and the antitumor activity of the estrogen antagonists is discussed.

L9 ANSWER 44 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:198657 HCAPLUS
DOCUMENT NUMBER: 102:198657
TITLE: 6-Oxo-prostaglandin F1.alpha. production by guinea pig skeletal muscle in vitro: the effects of estradiol and progesterone
AUTHOR(S): Kerry, P. J.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Edinburgh, Edinburgh, UK
SOURCE: Prostaglandins, Leukotrienes Med. (1985), 17(3), 283-9
CODEN: PLMEDD; ISSN: 0262-1746
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fragments of guinea pig skeletal **muscle** produced 4 times as much 6-oxo-PGF1.alpha. [58962-34-8] as prostaglandin (PG)E and PGF. This prodn. of 6-oxo-PGF1.alpha. was unaffected by relatively high concns. of 17.beta.-estradiol [50-28-2] (100 .mu.g/mL) but was increased 4-fold in the presence of progesterone [57-83-0] (500 .mu.g/mL). In skeletal **muscle** homogenates, estradiol (100 .mu.g/mL) inhibited 6-oxo-PGF1.alpha. synthesis, and this inhibition was enhanced in the presence of progesterone (500 .mu.g/mL); at this concn., progesterone had no effect of its own. Tamoxifen [**10540-29-1**] (100 .mu.g/mL) (an anti-estrogen in humans) enhanced the inhibition of 6-oxo-PGF1.alpha. synthesis by estradiol and by estradiol and progesterone together, suggesting that estradiol and tamoxifen may exert their effects by a similar mechanism in this exptl. model. The significance of these observations was discussed.
IT **10540-29-1**

RL: BIOL (Biological study)
(oxo-PGF1.alpha. formation by **muscle** inhibition by estradiol and progesterone enhancement by)

L9 ANSWER 45 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:29906 HCAPLUS
DOCUMENT NUMBER: 100:29906
TITLE: Smooth muscle cell of the canine prostate in spontaneous benign hyperplasia, steroid-induced hyperplasia and estrogen- or tamoxifen-treated dogs
AUTHOR(S): Bruengger, A.; Bartsch, G.; Hollinger, B. E.; Holly, B.; Rohr, H. P.
CORPORATE SOURCE: Inst. Pathol., Univ. Basel, Basel, CH-4056, Switz.
SOURCE: J. Urol. (Baltimore) (1983), 130(6), 1208-10
CODEN: JOURAA; ISSN: 0022-5347
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Smooth **muscle** cells of spontaneous and steroid-induced (by treating castrates with dihydrotestosterone [521-18-6] and estradiol [50-28-2]) hyperplastic prostates in dogs were analyzed by electron microscopic morphometry, and the results were compared to those obtained from estrogen- or tamoxifen [**10540-29-1**]-treated dogs as well as from untreated or castrated control dogs. The prostatic smooth **muscle** cells of the dog were activated by estrogen as well as by tamoxifen, which proves the estrogenic side-effect of the latter. In marked contrast to that, neither in the spontaneous nor in the steroid-induced prostatic hyperplasia could an activation of the smooth **muscle** cells be found. This is a most important difference from human benign prostatic hyperplasia, which limits the use of this animal model, and it explains the different reaction of human and canine prostatic hyperplasia to therapeutic hormonal manipulations.
IT **10540-29-1**
RL: BIOL (Biological study)
(smooth **muscle** cell activation in response to, in benign prostate gland hyperplasia in dog)

L9 ANSWER 46 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1983:119869 HCAPLUS
DOCUMENT NUMBER: 98:119869
TITLE: Antiestrogen-binding sites distinct from the estrogen receptor: subcellular localization, ligand specificity, and distribution in tissues of the rat
AUTHOR(S): Sudo, Katsuichi; Monsma, Frederick J., Jr.; Katzenellenbogen, Benita S.
CORPORATE SOURCE: Dep. Physiol. Biophys., Univ. Illinois, Urbana, IL, 61801, USA
SOURCE: Endocrinology (Baltimore) (1983), 112(2), 425-34
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Antiestrogen binding sites were fractionated with the microsomal fraction of the rat uterus with only very small amts. of high speed cytosol. These binding sites were present in the 800 g for 10 min or 12,000 g or 20,000 g for 30 min supernatants but were pelleted on centrifugation at 100,000 g or 180,000 g for 1 h. These sites were present in the 12,000 g supernatant fraction of almost all rat tissues examd. They were highest in concn. in the liver, uterus, esophagus, ovary, brain, and kidney; lower levels were found in the lung and spleen, and negligible amts. were seen in **muscle**, heart, and serum. These sites were not localized exclusively or primarily in estrogen target tissues and their level did not parallel that of the estrogen receptor, which was high only in the uterus and ovary and at lower levels in liver and kidney. Affinity for this binding site follows the order trans-tamoxifen [**13002-65-8**] .gtoreq. cis-tamoxifen [**10540-29-1**] > CI 628 [5863-35-4] > trans-hydroxytamoxifen [**65213-48-1**] > CI 628M [76313-96-7] > LY 117018 [63676-25-5]. Triphenylethylene antiestrogens lacking the

amine side chain did not bind to the antiestrogen-specific sites, but several tamoxifen analogs with altered basic side chains had affinities for these sites 4-10-fold greater than that of tamoxifen. Hence the affinity of different antiestrogens for this site did not parallel the potency of these compds. as antiestrogens or their affinity for the estrogen receptor. Antiestrogen-specific binding sites and estrogen receptor sites differed in their thermal stability, pH stability, and protease sensitivity and in their pattern of depletion from the 12,000 g supernatant fraction following estradiol administration. These sites may not be directly involved in the mediation of classically recognized estrogen antagonism of antiestrogens; however, the high affinity and wide distribution of the sites suggested that they might influence the action of antiestrogens in vivo, possibly in a passive manner, by altering the apparent distribution vol. of antiestrogens.

L9 ANSWER 47 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1982:556736 HCAPLUS
DOCUMENT NUMBER: 97:156736
TITLE: Adaptation of the human breast cancer cell line MCF-7 to serum free medium culture on extracellular matrix
AUTHOR(S): Jozan, S.; Tournier, J. F.; Tauber, J. P.; Bayard, F.
CORPORATE SOURCE: Dep. Endocrinol., Cent. Hosp. Univ., Toulouse, 31054, Fr.
SOURCE: Biochem. Biophys. Res. Commun. (1982), 107(4), 1566-70
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The human breast cancer cell line MCF-7 was adapted to grow in serum-free medium on an extracellular matrix produced by bovine corneal **endothelial** cells. The cells were continuously maintained in these conditions for >11 mo with the same doubling time as the original population grown on plastic dishes in presence of charcoal-treated fetal calf serum. insulin [9004-10-8] And epidermal growth factor [62229-50-9] stimulated cell proliferation. estradiol (E2) [50-28-2], dexamethasone, L-triiodothyronine, and prolactin had no effect. tamoxifen [**10540-29-1**] And estrone [53-16-7] inhibited cell multiplication. The inhibition by tamoxifen was rescued by 4% charcoal-treated fetal calf serum and E2 but not by E2 alone.

L9 ANSWER 48 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1982:193659 HCAPLUS
DOCUMENT NUMBER: 96:193659
TITLE: Hydroxylated antiestrogens: new pharmacological probes to investigate estrogen and antiestrogen action
AUTHOR(S): Jordan, V. Craig
CORPORATE SOURCE: Wisconsin Clin. Cancer Cent., Univ. Wisconsin, Madison, WI, 53792, USA
SOURCE: Horm. Antagonists (1982), 109-28. Editor(s): Agarwal, Manjul K. de Gruyter: Berlin, Fed. Rep. Ger.
CODEN: 47KBAK
DOCUMENT TYPE: Conference
LANGUAGE: English
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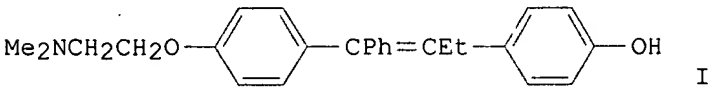
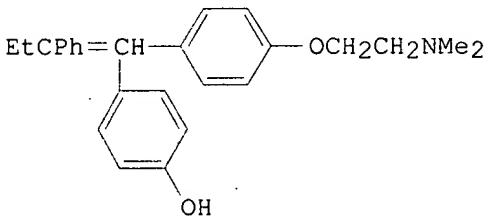


I

AB Receptor binding of 3H-labeled monohydroxytamoxifen (I) [**68047-06-3**] was investigated in vitro and in vivo. In rat uterus cytosol, I had .apprx.2-fold the affinity of estradiol [50-28-2] for estrogen receptors. Scatchard anal. revealed a Kd of 0.32 .times. 10-10M and 0.18 .times. 10-10M for estradiol and I, resp. Binding of I to the 8

S receptor of uterus cytosol was inhibited by DES but not by R 5020 or 5 .alpha.-dihydoxytestosterone. Administration of [3H]I or [3H]estradiol to immature rats resulted in radioactivity in the uterus but not in skeletal **muscle**. Moreover, the level of uterine radioactivity was maintained for a longer period after antiestrogen treatment than after estrogen. In ovariectomized rats, I bound to uterus, vagina, and pituitary; the binding was inhibited by pretreatment with tamoxifen. Apparently, there is little difference between the properties of the estrogen receptor bound with either estrogen or antiestrogen. A model for estrogen-antiestrogen action is given and a review of the development of and pharmacol. of antiestrogens is included.

L9 ANSWER 49 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1982:174674 HCAPLUS
DOCUMENT NUMBER: 96:174674
TITLE: Binding of [3H]monohydroxytamoxifen by immature rat tissues in vivo
AUTHOR(S): Jordan, V. Craig; Bowser-Finn, Ruth Ann
CORPORATE SOURCE: Wisconsin Clin. Cancer Cent., Univ. Wisconsin, Madison, WI, 53792, USA
SOURCE: Endocrinology (Baltimore) (1982), 110(4), 1281-91
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



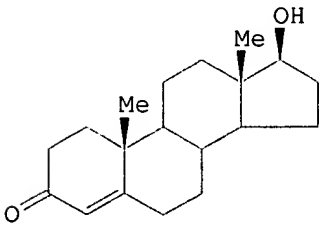
I

AB The distribution and tissue binding of 3H-labeled monohydroxytamoxifen (I) [**68047-06-3**] were detd. in the immature rat and compared with that obsd. with 3H-labeled estradiol [50-28-2]. [3H]I (20 .mu.Ci) produced a prolonged retention of radioactivity in the uterus, vagina, and liver for up to 48 h. Binding of radioactivity in the spleen, heart, and skeletal **muscle** was lower than that in the liver, uterus, and vagina, rose to maximal levels at 4 h, and decreased thereafter. In contrast [3H]estradiol (10 .mu.Ci) rapidly bound in the uterus and vagina (within 2 h) and rapidly decreased toward values in nontarget tissue (spleen, heart, and skeletal **muscle**) by 24 h. The levels of radioactivity in the blood after [3H]estradiol and [3H]I treatment reflected the pattern of radioactivity in the uterus and vagina. The binding of [3H]I in the uterus was inhibited by pretreatment of rats with the antiestrogens trioxifene [63619-84-1], tamoxifen [**10540-29-1**], and I and the estrogens estradiol and diethylstilbestrol [56-53-1]. By comparison, progesterone, 5.alpha.-dihydrotestosterone, and cortisol were ineffective. Similarly, estradiol, tamoxifen, and I, but not progesterone, 5.alpha.-dihydrotestosterone, and cortisol, inhibited estrogen-specific binding of [3H]estradiol and [3H]I by uterine cytosols in vitro. When different tissues were compared in vivo, increasing doses of I, but not estradiol, inhibited [3H]I binding in the liver. Both estradiol and I inhibited [3H]I binding in the uterus in a dose-related manner. Estradiol (10 .mu.g), diethylstilbestrol (100 .mu.g), or I (10 or 100 .mu.g) reversed the binding of prebound [3H]I by the uterus or vagina. In general, estrogen pretreatment was less effective at inhibiting the binding of [3H]I than antiestrogen pretreatment, suggesting either the demonstration of antiestrogen (estrogen-insensitive)-binding component of tissues or, more likely, major pharmacokinetic differences between

estrogens and antiestrogens.

L9 ANSWER 50 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1981:114777 HCAPLUS
DOCUMENT NUMBER: 94:114777
TITLE: High-affinity antiestrogen binding site distinct from the estrogen receptor
AUTHOR(S): Sutherland, Robert L.; Murphy, Leigh C.; Foo, Ming San; Green, Michael D.; Whybourne, Anne M.; Krozowski, Zygmunt S.
CORPORATE SOURCE: Ludwig Inst. Cancer Res., Univ. Sydney, Sydney, 2006, Australia
SOURCE: Nature (London) (1980), 288(5788), 273-5
CODEN: NATUAS; ISSN: 0028-0836
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cytosols of estrogen target tissues contained an excess of high-affinity, saturable, antiestrogen binding sites over estrogen receptors, and estradiol was unable to compete for all these sites, suggesting the existence of specific antiestrogen binding sites. These sites had high affinity (Kd 3-10 nM) for CI 628 [5863-35-4] and tamoxifen [**10540-29-1**] and were saturable at nanomolar concns. of the drugs. The binding sites showed considerable specificity, binding a series of structurally related synthetic nonsteroidal antiestrogens but not several steroid hormones. The sites were present in all estrogen target tissues studied but not in human mammary carcinoma lacking estrogen receptors, nor in rat plasma and skeletal **muscle**. The binding site was a protein and its concn. changed during the estrous cycle in the rat. This binding site may have a role in regulating the effects of nonsteroidal antiestrogens.

L9 ANSWER 51 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1980:598294 HCAPLUS
DOCUMENT NUMBER: 93:198294
TITLE: Comparative effects and mechanisms of castration, estrogen anti-androgen, and anti-estrogen-induced regression of accessory sex organ epithelium and muscle
AUTHOR(S): Neubauer, Blake; Blume, Cheryl; Cricco, Robert; Greiner, Jack; Mawhinney, Michael
CORPORATE SOURCE: Dep. Urol. Pharmacol., West Virginia Univ. Med. Cent., Morgantown, WV, USA
SOURCE: Invest. Urol. (1980), 18(3), 227-32
CODEN: INURAQ; ISSN: 0021-0005
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



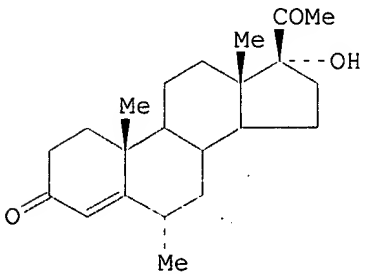
I

AB The effects and mechanisms of action of various endocrine manipulations on the epithelium and **muscle** prepns. of the guinea pig seminal vesicle were studied. Castration, which decreased the plasma testosterone (I) [58-22-0] level to 10% of normal, caused approx. 80% redns. in epithelium wet wt. and RNA and DNA contents. Estradiol benzoate [50-50-0] effected similar redns. in plasma androgen and epithelial cell

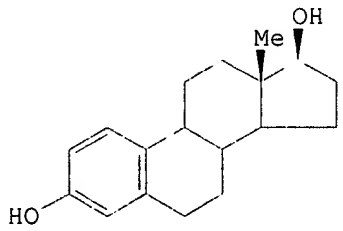
function in intact males. Redn. in plasma androgen level accounted for the estrogen-induced epithelial regression; no antiandrogenic effect of estrogen on the epithelium was detectable. All antiandrogens tested, flutamide [13311-84-7], spironolactone [52-01-7], and cyproterone acetate (II) [427-51-0] reduced epithelium wt. in intact animals. Studies of the mechanism of II action indicated its effects were attributable solely to an antiandrogenic action on the epithelium. The antiestrogens, tamoxifen [**10540-29-1**] and nafoxidine [1845-11-0] had no effect on the epithelium of intact animals when tested alone or in combination with II. Regression of seminal vesicle **muscle** occurred only after castration or treatment of intact animals with II. The action of II on the **muscle** was attributable to blockade of the androgenic stimulus. The drug had no effect on plasma I or estradiol [50-28-2] levels and had no antiestrogenic activity. In intact males estradiol reduced plasma I to castrate levels, but did not alter **muscle** wt. and nucleic acid levels. The potential deleterious effects of reduced plasma I on the **muscle** were prevented by direct estrogenic stimulation of the tissue. The antiandrogens, flutamide and spironolactone, and the antiestrogens, tamoxifen and nafoxidine, had no effect on the **muscle** of intact males. Inasmuch as the regressive effects of castration on the epithelium and **muscle** can be duplicated in intact animals only by treatment with II, this particular drug may provide the most effective nonsurgical treatment of prostatic neoplasia.

IT **10540-29-1**
RL: BIOL (Biological study)
(seminal vesicle epithelium and **muscle** response to)

L9 ANSWER 52 OF 52 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1979:16847 HCAPLUS
DOCUMENT NUMBER: 90:16847
TITLE: The effects of estradiol-17.beta., provera and tamoxifen on glucose metabolism in mammary gland, liver and muscle of the rat
AUTHOR(S): Deshpande, N.; Mitchell, Irene; Martin, L.
CORPORATE SOURCE: Endocrinol. Group, Imperial Cancer Res. Fund, London, Engl.
SOURCE: J. Steroid Biochem. (1978), 9(10), 995-9
CODEN: JSTBBK; ISSN: 0022-4731
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



II

AB The activities of 7 enzymes assocd. with glucose [50-99-7] metab. were measured in **muscle**, liver, and mammary glands of intact, castrated, and castrated rats treated with Provera (I acetate) [71-58-9], 17.beta.-estradiol (II) [50-28-2], or Tamoxifen [**10540-29-1**]. The following differences were obsd.: castration decreased the activities of glucose 6-phosphate dehydrogenase (G6PDH) [9001-40-5] and phosphoglucomutase (PGM) [9001-81-4] in the mammary glands whereas it increased total protein content of the tissue. Administration of I or II failed to alter these castration-induced changes. Tamoxifen treatment

decreased the castration-induced rise in total protein and PGM activity. Castration induced a decrease in the activity of 6-phosphogluconate dehydrogenase (6PGDH) [9001-82-5] and an increase in the activity of phosphohexose isomerase (PHI) [9001-41-6] in liver. Administration of II to castrated animals increased the activity of 6PGDH to the levels found in intact animals. Tamoxifen treatment caused a decrease in the activities of G6PDH, 6PGDH, and PHI. Neither castration nor any of the subsequent treatments affected glucose metab. in **muscle**.

IT **10540-29-1**
RL: BIOL (Biological study)
(glucose metab. response to, in liver and mammary gland and **muscle**, enzymes in relation to)

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=> d stat que l10 nos
L1             STR
L5          1782 SEA FILE=REGISTRY SSS FUL L1
L6             STR
L7           656 SEA FILE=REGISTRY SUB=L5 SSS FUL L6
L8          4553 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7
L9            52 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8(L)(ENDOTHEL? OR MUSCLE)
L10           40 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L8(L)(?DIABET? OR ?SURG? OR
                 ?HYPERTENS? OR ?CORONARY? OR ?ARTER? OR ?RESTEN? OR BLOOD(W)(PR
                 ESSURE OR SUGAR))) NOT L9


=> d ibib abs hitrn l10 1-40

L10  ANSWER 1 OF 40  HCAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         2000:659369  HCAPLUS
DOCUMENT NUMBER:          134:141542
TITLE:                    Acute treatment with tamoxifen reduces ischemic damage
                          following middle cerebral artery occlusion
AUTHOR(S):                Kimelberg, Harold K.; Feustel, Paul J.; Jin, Yiqiang;
                          Paquette, Justin; Boulos, Alan; Keller, Richard W.;
                          Tranmer, Bruce I.
CORPORATE SOURCE:         Division of Neurosurgery Department of Surgery, and
                          Center for Neuropharmacology and Neuroscience, Albany
                          Medical College, Albany, NY, 12208, USA
SOURCE:                   NeuroReport (2000), 11(12), 2675-2679
                          CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER:                Lippincott Williams & Wilkins
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
```

AB Inhibitors of cell-swelling-activated anion channels, including the antiestrogenic compd. tamoxifen (TAM), have been shown to attenuate the increase in excitatory amino acids (EAA) during ischemia. Since TAM enters the CNS we tested whether it provides protection from damage due to reversible middle cerebral artery occlusion (rMCAo) in rats. TAM (5 mg/kg, i.v.) infused 25 min before ischemia, potently reduced the total vol. of the infarct from 328 .+-. 34 mm3 to 41 .+-. 21 mm3, a redn. of 87%, as measured by TTC staining. It was equally effective when infused starting at I h after reperfusion, i.e. 3 h after initiation of rMCAo. Protection of neurons was also found histol. TAM had no effect on CBF as measured by hydrogen clearance. This appears to be the first report of a marked neuroprotective effect of TAM. Further studies are needed to det. whether its effects are due to inhibition of EAA release and/or other potential neuroprotective sites of action.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tamoxifen treatment reduces ischemic damage following middle cerebral **artery** occlusion)

REFERENCE COUNT: 26
REFERENCE(S): (2) Biegon, A; Cancer Res 1996, V56, P4328 HCAPLUS
(3) Chan, P; Cerebral Ischemia: Molecular and Cellular

Pathophysiology 1999, P105 HCAPLUS
(4) Dawson, T; Neuroscientist 1998, V4, P96 HCAPLUS
(6) Dubey, R; Circ Res 1999, V84, P229 HCAPLUS
(7) Garcia, J; J Membr Biol 1998, V162, P59 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:493381 HCAPLUS
DOCUMENT NUMBER: 133:100053
TITLE: Use of estrogens and delta-gonadien-21-ol-3,20-diones for treating insulin dependent and non-insulin dependent diabetes
INVENTOR(S): Wassermann, Karsten
PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000041701	A1	20000720	WO 2000-DK21	20000117

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DK 1999-51 A 19990118
AB The present invention relates to the use of a combination of estrogens or SERMs with delta-gonadien-21-ol-3,20-diones for treating diabetes, particularly type II diabetes. It also embraces pharmaceutical compns. and kits comprising these compds. and methods of using the compds. and their pharmaceutical compns.
IT **10540-29-1**, Tamoxifen **68047-06-3**, 4-Hydroxytamoxifen
82413-20-5, Droloxifene
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of estrogens or SERMs in combination with delta-gonadien-21-ol-3,20-diones in treatment of **diabetes**)
REFERENCE COUNT: 3
REFERENCE(S): (1) American Home Products Corporation; WO 9804246 A2 1998 HCAPLUS
(2) Robinson, J; Diabetes Care May V19(5), P480 MEDLINE
(3) Tchernof, A; Coron Artery Dis 1998, V9(8), P503 MEDLINE

L10 ANSWER 3 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:237935 HCAPLUS
Correction of: 1997:183424
DOCUMENT NUMBER: 132:231895
Correction of: 126:220634
TITLE: Potent inhibition by tamoxifen of spontaneous and agonist-induced contractions of the human myometrium and intramyometrial arteries
AUTHOR(S): Kostrzewska, Anna; Laudanski, Tadeusz; Batra, Satish
CORPORATE SOURCE: Institute of Obstetrics and Gynaecology, Bialystok, Pol.
SOURCE: Am. J. Obstet. Gynecol. (1997), 176(2), 381-386
CODEN: AJOGAH; ISSN: 0002-9378

PUBLISHER: Mosby-Year Book
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mechanism of the direct action of antiestrogens on spontaneous and agonist-induced contractions of the human myometrium and uterine arteries was studied. Myometrial strips and pieces of uterine arteries were obtained from nonpregnant premenopausal women undergoing hysterectomy. The spontaneous activity of the myometrium and the responses of the myometrium and arteries to K+-induced depolarization and vasopressin were recorded under isometric conditions. For spontaneous myometrial activity, the 50% inhibitory concns. of tamoxifen, clomiphene, and cyclofenil were 2.8, 43, and 331 nM, resp. Vasopressin-induced contractions in both the myometrium and arteries were potently inhibited by tamoxifen, and the 50% inhibitory concn. for the myometrium (1.4 nM) was lower than that for the arteries (11 nM). Although tamoxifen caused no inhibition of responses induced by high KCl (80 mM), responses induced by low KCl (20 mM) were inhibited 40%-50% in both the myometrium and arteries. Glibenclamide reversed the inhibition of spontaneous myometrial activity by tamoxifen. Thus, tamoxifen is a highly potent inhibitor of the contractile activity of the human nonpregnant myometrium and uterine arteries. Tamoxifen may have strong potential for the treatment of dysmenorrhea.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(contractions of human myometrium and intramyometrial **arteries** inhibition by)

L10 ANSWER 4 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:235525 HCAPLUS
DOCUMENT NUMBER: 132:330106
TITLE: Vascular actions of 17.beta.-estradiol in rat aorta and mesenteric artery
AUTHOR(S): Browne, M.; Connolly, C.; Docherty, J. R.
CORPORATE SOURCE: Department of Physiology, Royal College of Surgeons in Ireland, Dublin, Ire.
SOURCE: J. Auton. Pharmacol. (1999), 19(5), 291-299
CODEN: JAPHDU; ISSN: 0144-1795
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It has been proposed that the cardiovascular protective actions of 17.beta.-estradiol may involve calcium antagonistic actions. The authors have examd. the effects of 17.beta.-estradiol on contractions to noradrenaline and KCl in male rat small mesenteric artery and aorta. In rat mesenteric artery, 17.beta.-estradiol (10 .mu.M) significantly reduced the max. contraction to noradrenaline (67.7% of control) and KCl (38.8% of control) without affecting potency. In rat aorta, 17.beta.-estradiol (10 .mu.M) also significantly reduced contractions to noradrenaline (77.5% of control), and the effects were mimicked by droloxifene (10 .mu.M). In expts. carried out in calcium-free soln. in which calcium stores were depleted, 17.beta.-estradiol (10 .mu.M) significantly reduced the contraction to calcium restoration in rat aorta. In aorta from female rats, 17.beta.-estradiol (10 .mu.M) significantly reduced contractions to noradrenaline (73.6% of control), but this effect of estrogen was not prevented by cycloheximide (10 .mu.M). In summary, 17.beta.-estradiol diminishes the max. contractile response to noradrenaline in both rat small mesenteric artery and aorta, an effect which at least in the aorta is mimicked by the estrogen receptor antagonist/partial agonist droloxifene, and may be due to restriction of calcium entry by a nongenomic action.

IT **82413-20-5**, Droloxifene
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(estradiol attenuation of aorta and mesenteric **artery** contraction in relation to calcium antagonism)

L10 ANSWER 5 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:671010 HCAPLUS
DOCUMENT NUMBER: 131:282020
TITLE: Method for the prevention of coronary artery spasm using an antiestrogen
INVENTOR(S): Kanda, Iwao
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 4 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5968918	A	19991019	US 1997-953340	19971017

AB The present invention relates to the prevention of coronary artery spasm in mammals by the administration of an effective amt. of an antiestrogen compd. to block estrogen receptors for the redn. or prevention of the formation of an estrogen--estrogen receptor complex so that estrogen response elements in the DNA of the smooth muscle of the coronary arteries is not activated by the complex. The method of the invention is used to reduce the risk of spasm induced cardiac problems such as sudden infant death syndrome. The antiestrogen is selected from the group consisting of progestins and nonsteroidal antiestrogen compds. For example to reduce the risk of a SIDS incident, one cc of an aq. soln. of medroxyprogesterone acetate (150 .mu.g/mL) is administered as a single fetal injection during the 36th to 39th week of gestation.

IT **10540-29-1**, Tamoxifen **82413-20-5**, Droloxifene
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for prevention of **coronary artery** spasm using an antiestrogen)

REFERENCE COUNT: 5
REFERENCE(S):
(1) Anon; US 5512557 1996 HCAPLUS
(2) Grainger; US 5472985 1995 HCAPLUS
(3) Kanda, I; Medical Hypothesis 1997, V49, P183 MEDLINE
(4) Knuz; US 5733925 1998 HCAPLUS
(5) Young; US 4729999 1988 HCAPLUS

L10 ANSWER 6 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:252831 HCAPLUS
DOCUMENT NUMBER: 131:68254
TITLE: p53 expression in breast and endometrium during estrogen and tamoxifen treatment of surgically postmenopausal cynomolgus macaques
AUTHOR(S): Isaksson, E.; Cline, J. M.; Skoog, L.; Soderqvist, G.; Wilking, N.; Von Schoultz, E.; Von Schoultz, B.
CORPORATE SOURCE: Department of Oncology, Radiumhemmet, Karolinska Hospital, Stockholm, Swed.
SOURCE: Breast Cancer Res. Treat. (1999), 53(1), 61-67
CODEN: BCTRD6; ISSN: 0167-6806
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Estrogens are important for both normal cell growth and malignant proliferation in the mammary gland as well as in the endometrium. Tamoxifen is a non-steroidal anti-estrogen widely used in breast cancer treatment. In recent years reports have been made of an increased risk of endometrial carcinoma during tamoxifen treatment. The authors used surgically menopausal cynomolgus macaques to study proliferation and p53 expression during hormonal replacement therapy (HRT) and tamoxifen treatment. Animals were treated continuously for 35 mo with either conjugated equine estrogens (CEE; n = 20); medroxyprogesterone acetate

(MPA; n = 17); the combination of CEE + MPA (n = 13); or tamoxifen (n = 17) for 35 mo. The authors found an increased expression of p53 in normal breast and endometrial tissue linked to CEE but not tamoxifen treatment. In the breast alveoli there was an assocn. between proliferation measured by morphometry and p53 expression in all groups. However, in the endometrium CEE induced significantly more p53 positivity than tamoxifen, 9/20 vs. 3/17 in glands and 9/19 vs. 0/17 in stroma, resp. If indeed long-term treatment with tamoxifen as in the present study could inactivate the tumor-suppressive function of p53, endometrial cells might thereby become more susceptible to genetic lesions assocd. with carcinogenesis.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(p53 expression in breast and endometrium during estrogen and tamoxifen treatment of **surgically** postmenopausal cynomolgus macaques)

REFERENCE COUNT: 40
REFERENCE(S):
(1) Adams, M; Arteriosclerosis Thrombosis & Vascular Biology 1997, V17, P217 HCAPLUS
(2) Boccuzzi, A; Anticancer Res 1995, V15, P1407 HCAPLUS
(4) Cline, J; Am J Obstet Gynecol 1996, V174, P93 HCAPLUS
(10) Greenblatt, M; Cancer Res 1994, V54, P4855 HCAPLUS
(11) Gudas, J; Cell Growth Diff 1994, V5, P295 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:532361 HCAPLUS
DOCUMENT NUMBER: 129:254716
TITLE: Lack of effect of raloxifene on coronary atherosclerosis of postmenopausal monkeys. Reply to comments
AUTHOR(S): Clarkson, Thomas B.; Anthony, Mary S.
CORPORATE SOURCE: Wake Forest University School of Medicine, Winston-Salem, NC, 27157, USA
SOURCE: J. Clin. Endocrinol. Metab. (1998), 83(8), 3002-3004
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A polemic in answer to Henry U. Bryant et al (ibid. 83:3001-3002,1998).
IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lack of effect of raloxifene on **coronary** atherosclerosis of postmenopausal monkeys)

L10 ANSWER 8 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:456303 HCAPLUS
DOCUMENT NUMBER: 129:225873
TITLE: Estrogen protects against while testosterone exacerbates vulnerability of the lateral striatal artery to chemical hypoxia by 3-nitropropionic acid
AUTHOR(S): Nishino, Hitoo; Nakajima, Keiya; Kumazaki, Michiko; Fukuda, Atsuo; Muramatsu, Kanji; Deshpande, Shripad B.; Inubushi, Toshiro; Morikawa, Shigehiro; Borlongan, Cesario V.; Sanberg, Paul R.
CORPORATE SOURCE: Department of Physiology, Nagoya City University Medical School, Mizuho-chio, Mizuho-ku, Nagoya, 467, Japan
SOURCE: Neurosci. Res. (Shannon, Irel.) (1998), 30(4), 303-312
CODEN: NERADN; ISSN: 0168-0102
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Gender differences in the vulnerability of the lateral striatal artery (ISTR artery) to systemic intoxication with 3-nitropropionic acid (3-NPA, succinate dehydrogenase inhibitor) were studied. S.c. injection of 3-NPA (20 mg/kg once a day for 2 days) induced striatal selective lesions in half of male rats assocd. with motor symptoms (rolling, paddling, recumbency, etc.) while female rats were resistant. Lesions were located in the lateral striata and characterized by astroglial necrotic cell death, enhanced immunoreaction to factor VIII-related antigen, edema, extravasation of IgG and sometimes bleeding. The motor and histol. disturbances were highly sex-dependent and modulated by changes in hormonal levels. Males were more susceptible than females. Castration had little effect but ovariectomy enhanced the vulnerability. Replacement therapy with testosterone increased while estradiol or tamoxifen suppressed the vulnerability in ovariectomized females. Investigation of the arterial architecture of the brain often revealed rectangular and acute angled branchings in the centrolateral striatum where the ISTR artery feeds. A parallel in vitro toxicity study demonstrated that an extreme Ca++ overload and a strong cellular swelling resulted in astrocytic cell death. Data suggest that ISTR artery and astrocytes are highly vulnerable to 3-NPA intoxication in males. The greater vulnerability of the ISTR artery may contribute to the pathogenesis of neurodegenerative diseases, striatal bleeding, etc. Protective effects of estrogen and tamoxifen may mediate gender differences often obsd. in these disorders and suggest their potential use as therapeutic agents for these disorders.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(estrogen protects against while testosterone exacerbates vulnerability of lateral striatal **artery** to chem. hypoxia by 3-nitropropionic acid)

L10 ANSWER 9 OF 40 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:400143 HCAPLUS
DOCUMENT NUMBER: 129:174063
TITLE: An experimental model of diabetes and cancer in rats
AUTHOR(S): Cocca, C.; Martin, G.; Rivera, E.; Davio, C.; Cricco, G.; Lemos, B.; Fitzsimons, C.; Gutierrez, A.; Levin, E.; Levin, R.; Croci, M.; Bergoc, R. M.
CORPORATE SOURCE: Laboratorio de Radioisotopos, Catedra de Fisica, Facultad de Farmacia y Bioquimica, Universidad de Buenos Aires, Buenos Aires, Argent.
SOURCE: Eur. J. Cancer (1998), 34(6), 889-894
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of this study was to develop an exptl. model for the study of cancer assocd. with diabetes. For diabetes induction, Sprague-Dawley rats were given streptozotocin (STZ, 90 mg/kg body wt. (BW)), by i.p. injection on the second day of life. For mammary tumor induction, rats were injected with 50 mg/kg BW of N-nitroso-N-methylurea (NMU) at 50, 80 and 110 days old. The neoplastic process and the effect of tamoxifen treatment was examd. in non-diabetic and diabetic rats. The latency period, NMU-induced tumor incidence and the no. of tumors per rat in diabetic rats vs. controls were 117 days vs. 79 days; 93% vs. 95% (NS); and 5.2 vs. 2.7. A more benign histol. pattern for tumors in diabetic animals was obsd. Mammary tumors in diabetic rats grew more slowly than in controls. Tamoxifen (1 mg/kg/day) treated diabetic rats showed tumor regression in 67% of NMU-induced mammary tumors vs. 53% in controls (NS). The authors' results show that tumor progression seems to be affected by diabetes in this exptl. model. The authors suggest this is the result of changes to insulin-like growth factors and their receptors, which occur in diabetics, and the authors' future research will examine this hypothesis.

IT **10540-29-1**, Tamoxifen

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(exptl. model of **diabetes** and cancer in rats in relation to tamoxifen treatment and insulin-like growth factors and receptors)

L10 ANSWER 10 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:329623 HCAPLUS
DOCUMENT NUMBER: 129:90040
TITLE: The effect of tamoxifen and transdermal 17.beta.-estradiol on cerebral arterial vessels: a randomized controlled study
AUTHOR(S): Penotti, M.; Sironi, L.; Miglierina, L.; Farina, M.; Barletta, L.; Gabrielli, L.; Vignali, M.
CORPORATE SOURCE: Second Obstetrical and Gynecological Department and the Institute of Vascular Surgery, University of Milano, Milan, 20122, Italy
SOURCE: Am. J. Obstet. Gynecol. (1998), 178(4), 801-805
CODEN: AJOGAH; ISSN: 0002-9378
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Our objective was to study the effects of tamoxifen on cerebral arterial reactivity. We studied the reactivity of both the internal carotid artery and the middle cerebral artery during a 12-mo period of administration of either oral tamoxifen or transdermal estradiol or no treatment. A total of 45 healthy postmenopausal women who had undergone hysterectomy were followed up. Patients were randomly allocated to treatment with either oral tamoxifen 20 mg/day or transdermal estradiol 50 .mu.g/day or nothing (15 patients in each group). They all underwent Doppler examns. of the internal carotid artery and middle cerebral artery at the beginning of the study and after 2, 6, and 12 mo of treatment. The pulsatility index was measured. In the women given transdermal estradiol, the pulsatility index of both the internal carotid artery and the middle cerebral artery was significantly reduced compared with that in the controls. Tamoxifen did not induce variations of pulsatility index in either artery during all the study period. The difference between the effect of the 2 drugs on the pulsatility index of both arteries was highly significant. Tamoxifen does not cause any variation in the pulsatility index of cerebral arteries. The action of transdermal estradiol on the pulsatility index of cerebral arteries in postmenopausal women is the expression of a generalized action of estrogens on arterial vessels, and if this expression plays a role in the protective effect of hormone replacement therapy on risk of cardiovascular disease, tamoxifen treatment in healthy postmenopausal women should be considered with renewed caution.
IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tamoxifen and transdermal estradiol effect on cerebral **arterial** vessels in controlled study)

L10 ANSWER 11 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:644156 HCAPLUS
DOCUMENT NUMBER: 127:288367
TITLE: Contrasting effects of conjugated estrogens and tamoxifen on dilator responses of atherosclerotic epicardial coronary arteries in nonhuman primates
AUTHOR(S): Williams, J. Koudy; Honore, Erika K.; Adams, Michael R.
CORPORATE SOURCE: Compar. Med. Clin. Res. Cent., Dep. Compar. Med., Bowman Gray Sch. Med., Wake Forest Univ., Winston-Salem, NC, USA
SOURCE: Circulation (1997), 96(6), 1970-1975
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Estrogens have been shown to improve dilator responses of atherosclerotic coronary arteries. Tamoxifen is a mixed estrogen agonist/antagonist with a yet unexplored effects on vascular function. Therefore, the goal of this study was to compare the effects of conjugated equine estrogens (CEEs) with those of tamoxifen on epicardial coronary artery dilator responses in atherosclerotic, ovariectomized monkeys. Fifty ovariectomized cynomolgus monkeys were fed an atherogenic diet for 34 mo. During this time, monkeys were assigned to one of three treatment groups: (1) control, no hormone replacement; (2) CEEs mixed in the diet at a dose of 0.043 mg.cntdot.kg-1.cntdot.d-1; or (3) tamoxifen mixed in the diet at a dose of 1.3 mg.cntdot.kg-1.cntdot.d-1. Quant. angiog. was used to measure coronary artery dilator responses to intracoronary infusions of acetylcholine (10-8, 10-7, and 10-6 mol/L) and nitroglycerin (15 .mu.g/min). Coronary arteries of the tamoxifen-treated group constricted in response to high-dose acetylcholine (-5.4.+-.2.3%, vs. control), whereas those of the CEE group did not (vs. control). Conversely, arteries from the CEE group dilated in response to nitroglycerin (9.1.+-.2.1%, vs. control), whereas those from the tamoxifen group did not (O>.05 vs. control). Statistical adjustments for variations in plaque extent (detd. subsequently after necropsy) and plasma lipoproteins did not alter the results. Tamoxifen has primarily estrogen-antagonistic effects on epicardial coronary artery dilator responses in atherosclerotic monkeys. Results implicate the estrogen receptor as a modulator of coronary artery dilator responses in ovariectomized atherosclerotic monkeys.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(contrasting effects of conjugated estrogens and tamoxifen on dilator responses of atherosclerotic epicardial **coronary arteries** in nonhuman primates)

L10 ANSWER 12 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:404608 HCAPLUS
DOCUMENT NUMBER: 127:60325
TITLE: Coronary heart disease mortality and adjuvant tamoxifen therapy
AUTHOR(S): Costantino, Joseph P.; Kuller, Lewis H.; Ives, Diane G.; Fisher, Bernard; Dignam, James
CORPORATE SOURCE: Department of Biostatistics, University of Pittsburgh, Pittsburgh, PA, 15261, USA
SOURCE: J. Natl. Cancer Inst. (1997), 89(11), 776-782
CODEN: JNCIEQ; ISSN: 0027-8874
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Data from randomized clin. trials in Scotland and Sweden testing the efficacy of tamoxifen therapy in patients with breast cancer have suggested that the drug may also reduce the risk of coronary heart disease. In view of these findings, the authors examd. mortality from coronary heart disease among patients with early stage breast cancer who were enrolled in the National Surgical Adjuvant Breast and Bowel Project B-14 trial of tamoxifen therapy. Deaths occurring among women who were randomly assigned to 5 yr of either tamoxifen or placebo in the first phase of the B-14 trial were reviewed to det. the cause. Three categories of heart disease-related death were defined: (1) death from a definite fatal myocardial infarction, (2) death from definite fatal coronary heart disease/possible myocardial infarction, and (3) death from possible fatal coronary heart disease. Comparisons of the findings by treatment group were made on the basis of av. annual hazard (i.e., death) rates and the corresponding relative hazard of death. The av. annual death rate from coronary heart disease was lower for patients who received tamoxifen than for patients who received placebo, but the difference was not statistically significant. There were eight definite heart-related deaths (i.e., definite fatal myocardial infarction or definite fatal coronary heart disease/possible myocardial infarction) among the patients who

received tamoxifen, yielding an av. annual rate of 0.62 per 1000 patients. There were 12 definite heart-related deaths among the patients who received placebo, yielding an av. annual rate of 0.94 per 1000. The corresponding relative hazard of death from definite fatal heart disease (tamoxifen vs. placebo) was 0.66 (95% confidence interval = 0.27-1.61). Eleven deaths in the tamoxifen group and 10 deaths in the placebo group were classified as possible cases of fatal coronary heart disease. When these cases and the definite cases were considered together, the av. annual death rate for the patients who received tamoxifen was 1.48 per 1000, and the rate for the patients who received placebo was 1.73 per 1000. The corresponding relative hazard of death was 0.85 (95% confidence interval = 0.46-1.58). The findings from the B-14 trial are consistent with the findings from the Scottish and the Swedish trials, suggesting that tamoxifen treatment reduces coronary heart disease among patients with breast cancer. Continued follow-up of the patients in these trials and in ongoing prevention trials is needed to accumulate enough data so that reliable conclusions can be drawn about the benefits of tamoxifen in preventing heart disease.

IT **10540-29-1**, Tamoxifen
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**coronary** heart disease mortality and adjuvant tamoxifen therapy in humans)

L10 ANSWER 13 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:194013 HCAPLUS
DOCUMENT NUMBER: 126:246599
TITLE: Tamoxifen inhibits arterial accumulation of LDL degradation products and progression of coronary artery atherosclerosis in monkeys
AUTHOR(S): Williams, J. Koudy; Wagner, Janice D.; Li, Zhang; Golden, Deborah L.; Adams, Michael R.
CORPORATE SOURCE: Comparative Medicine Clinical Research Center, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, NC, 27157-1040, USA
SOURCE: Arterioscler., Thromb., Vasc. Biol. (1997), 17(2), 403-408
CODEN: ATVBFA; ISSN: 1079-5642
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Estrogen replacement therapy reduces the risk of coronary heart disease in postmenopausal women and inhibits progression of coronary artery atherosclerosis in monkeys. Tamoxifen is a nonsteroidal compd. with mixed estrogen agonist and antagonist properties. Its antagonist activity is useful in chemotherapy of breast cancer and may have protective effects on plasma lipid concns., but its effects on atherogenesis have not been defined. The goal of this study was to examine the effect of tamoxifen on plasma lipids, arterial and hepatic LDL metab., and progression of coronary artery atherosclerosis in surgically postmenopausal female monkeys. Thirty-five monkeys were fed an atherogenic diet contg. 1.3 mg.cntdot.kg-1.cntdot.d-1 tamoxifen (equiv. to the usual dose of 20 mg/d given to women). Thirty-one monkeys were fed the same atherogenic diet with no tamoxifen. Ten monkeys from each treatment group were fed the test diets for 12 wk to examine the short-term effects of tamoxifen on arterial LDL metab. The rest of the monkeys were fed the test diets for 3 yr to study the long-term effects of tamoxifen on development of atherosclerosis. In the short term, tamoxifen inhibited the rate of arterial accumulation of LDL degrdn. products overall and decreased hepatic cholesterol content. In the long term, tamoxifen increased plasma concns. of triglycerides (0.60.+-.0.67 vs. 0.23.+-.0.02 mmol/L) and reduced av. LDL mol. wt. (5.3.+-.0.2 vs. 4.8.+-.0.1 g/.mu.mol) but had no effects on plasma total, LDL, or HDL cholesterol concns. Coronary artery atherosclerosis (intimal area) was 0.25.+-.0.06 mm2 in control monkeys and 0.12.+-.0.03 mm2 in tamoxifen-treated monkeys. We conclude that tamoxifen

has antiatherogenic effects that may be modulated in part through direct effects on arterial LDL metab.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tamoxifen inhibits **arterial** accumulation of LDL degrdn. products and progression of **coronary artery** atherosclerosis in monkeys)

L10 ANSWER 14 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:183424 HCAPLUS
DOCUMENT NUMBER: 126:220634
TITLE: Potent inhibition by tamoxifen of spontaneous and agonist-induced contractions of the human myometrium and intramyometrial arteries
AUTHOR(S): Kostrzewska, Anna; Laudanski, Tadeusz; Satish Batra
CORPORATE SOURCE: Institute of Obstetrics and Gynaecology, Medical Academy, University Hospital, Bialystok, Pol.
SOURCE: Am. J. Obstet. Gynecol. (1997), 176(2), 381-386
CODEN: AJOGAH; ISSN: 0002-9378
PUBLISHER: Mosby-Year Book
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mechanism of the direct action of antiestrogens on spontaneous and agonist-induced contractions of the human myometrium and uterine arteries was studied. Myometrial strips and pieces of uterine arteries were obtained from nonpregnant premenopausal women undergoing hysterectomy. The spontaneous activity of the myometrium and the responses of the myometrium and arteries to K+-induced depolarization and vasopressin were recorded under isometric conditions. For spontaneous myometrial activity, the 50% inhibitory concns. of tamoxifen, clomiphene, and cyclofenil were 2.8, 43, and 331 nM, resp. Vasopressin-induced contractions in both the myometrium and arteries were potently inhibited by tamoxifen, and the 50% inhibitory concn. for the myometrium (1.4 nM) was lower than that for the arteries (11 nM). Although tamoxifen caused no inhibition of responses induced by high KCl (80 mM), responses induced by low KCl (20 mM) were inhibited 40%-50% in both the myometrium and arteries. Glibenclamide reversed the inhibition of spontaneous myometrial activity by tamoxifen. Thus, tamoxifen is a highly potent inhibitor of the contractile activity of the human nonpregnant myometrium and uterine arteries. Tamoxifen may have strong potential for the treatment of dysmenorrhea.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(contractions of human myometrium and intramyometrial **arteries** inhibition by)

L10 ANSWER 15 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:126984 HCAPLUS
DOCUMENT NUMBER: 124:165616
TITLE: Effect of gender and sex steroids on the contractile response of canine coronary and renal blood vessels
AUTHOR(S): Karanian, John W.; Ramwell, Peter W.
CORPORATE SOURCE: Lab. Membrane Biochem. Biophys., NIAAA, Washington, DC, USA
SOURCE: J. Cardiovasc. Pharmacol. (1996), 27(3), 312-19
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of gender, gonadal steroids, and antiandrogen/antiestrogen-treatment on the isotonic response of isolated prepns. of the left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), and renal artery and vein of sexually mature dogs was investigated. The max. isotonic response of the coronary and renal vasculature to the thromboxane A2 (TXA2)-mimetic U46619 was significantly greater, and the EC50 value was significantly lower in males as compared with females.

Moreover, similar gender differences in the contractile response of the coronary vasculature to norepinephrine were obsd. Pretreatment of male dogs with the antiandrogens flutamide or cyproterone acetate reduced the max. contractile response of the LAD to the TXA2-mimetic. Pretreatment of female dogs with testosterone resulted in an increase in both the max. contractile response and EC50 value to U46619. Antiestrogen treatment of female dogs with tamoxifen was assocd. with an increase in the max. contractile response of the LAD to U46619. Estrogen pretreatment of male dogs decreased both the max. contractile response and the EC50 value to U46619. Therefore, there is a sex difference in LAD and LCX contractile responses to both U46619 and norepinephrine. These results suggest that smooth muscle reactivity of dog coronary artery to the TXA2-mimetic U46619 may be susceptible to regulation by both androgens and estrogens. The obsd. gender differences in the catecholamine response may be similarly altered by changes in the hormonal milieu.

IT **10540-29-1**, Tamoxifen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(gender and sex steroids effects on contractile response of canine **coronary** and renal blood vessels to norepinephrine and TXA2)

L10 ANSWER 16 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:40896 HCAPLUS
DOCUMENT NUMBER: 124:134992
TITLE: Long-term follow-up of elderly patients with operable breast cancer treated with surgery without axillary dissection plus adjuvant tamoxifen
AUTHOR(S): Martelli, G; DePalo, G; Rossi, N; Coradini, D; Boracchi, P; Galante, E; Vetrella, G
CORPORATE SOURCE: Divisions Diagnostic Oncology and Outpatient Clinic, Istituto Nazionale Tumori, Milan, 20133, Italy
SOURCE: Br. J. Cancer (1995), 72(5), 1251-5
CODEN: BJCAAI; ISSN: 0007-0920
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Between 1982 and 1990, 321 elderly patients (range 70-92 yr, median age 77) with operable breast cancer (T1 in 219, T2 in 77, T3 in one and T4b in 24 patients) and clin. uninvolved axillary nodes underwent surgery without axillary dissection and received adjuvant tamoxifen. All patients had surgery performed under local anesthesia. Tamoxifen was given after surgery at the dose of 20 mg daily, indefinitely. With a median follow-up of 67 mo (range 42-141), 17 patients developed local relapse, 14 ipsilateral axillary recurrence, five ipsilateral breast cancer, five contralateral breast cancer, 13 s primary and 23 developed distant metastases. The cumulative probability of developing a local, axillary and distant recurrence at 72 mo was estd. to be 5.4%, 4.3% and 6.2%, resp. Out of 244 patients who did not develop any relapse, 83 (25.8%) died from intercurrent disease. The 72 mo relapse-free survival rate was 76%. This experience suggests that elderly patients with small tumors without clin. axillary involvement may be satisfactorily treated with conservative surgery and tamoxifen. The importance of axillary dissection is controversial owing to a high response rate to hormonal therapy and an increased death rate due to concomitant diseases.

IT **10540-29-1**, Tamoxifen
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long-term follow-up of elderly humans with operable breast cancer treated with **surgery** without axillary dissection plus adjuvant tamoxifen)

L10 ANSWER 17 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1989:526576 HCAPLUS
DOCUMENT NUMBER: 111:126576
TITLE: Chemopreventive efficacy of combined retinoid and tamoxifen treatment following surgical excision of a

primary mammary cancer in female rats
AUTHOR(S): Ratko, Thomas A.; Detrisac, Carol J.; Dinger, Nancy M.; Thomas, Cathy F.; Kelloff, Gary J.; Moon, Richard C.
CORPORATE SOURCE: Res. Inst., IIT, Chicago, IL, 60616, USA
SOURCE: Cancer Res. (1989), 49(16), 4472-6
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Dietary N-(4-hydroxyphenyl)retinamide (4-HPR; 3 mmol/kg diet) and s.c. injections of the antiestrogen tamoxifen (Tx; 10 or 20 .mu.g/rat, thrice weekly) were used together as adjunct chemopreventive therapy after surgical removal of tumors in female rats that each received an i.v. injection (50 mg/kg) of the mammary gland carcinogen N-methyl-N-nitrosourea (MNU). The treatment was started immediately following the surgical excision of the first (primary) mammary carcinoma from each MNU-treated rat and was continued for 180 days. When compared to the effects of treatment with 4-HPR or Tx (30 .mu.g/wk) alone, the combination enhanced terminal survival and reduced nonrecurrent mammary cancer incidence and multiplicity. The occurrence of 1-5 addnl. cancers after the surgical resection of the primary lesion demonstrated that the combined treatment with 4-HPR/Tx was immediately and consistently more effective than either agent alone in suppressing the subsequent tumor appearance. This effect was apparently related to the dose of Tx. The combined treatment with 4-HPR/Tx is superior to that of either agent alone in blocking progression of incipient neoplastic lesions at both early and later stages of the process.
IT **10540-29-1**, Tamoxifen
RL: BIOL (Biological study)
(mammary carcinoma inhibition by hydroxyphenylretinamide and, after **surgical** excision)

L10 ANSWER 18 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:207327 HCAPLUS
DOCUMENT NUMBER: 106:207327
TITLE: Synergistic action of lentinan (LNT) with endocrine therapy for breast cancer in rats and humans
AUTHOR(S): Kosaka, Akio; Kuzuoka, Masahiko; Yamafuji, Kazuo; Imaizumi, Atsuko; Hattori, Yuuichi; Yamashita, Akira
CORPORATE SOURCE: Div. Surg., Shimizu City Hosp., Japan
SOURCE: Gan to Kagaku Ryoho (1987), 14(2), 516-22
CODEN: GTKRDX; ISSN: 0385-0684
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB The effect of lentinan (LNT) [37339-90-5] was investigated in rats with DMBA-induced mammary tumors and also in patients with recurrent breast cancer. LNT injection following **surgical** therapy resulted in a much greater regression of tumor growth than that obtained by **surgery** alone, but not greater than that after therapy with tamoxifen [**10540-29-1**]. LNT-**surgical** therapy resulted in marked atrophy of tumors and intense infiltration of T cells, B cells and macrophages into the stroma around the tumor. Blood prolactin level was greatly reduced by LNT injection. A clin. randomized controlled study demonstrated the efficacy and safety of LNT following **surgery** in patients with recurrent breast cancer. The mode of the synergistic action of LNT in combination with endocrine therapy on hormone-dependent tumors is discussed.

L10 ANSWER 19 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:189278 HCAPLUS
DOCUMENT NUMBER: 106:189278
TITLE: Polyamine modification in human breast tumors after short treatment with tamoxifen
AUTHOR(S): Messeri, G.; Quercioli, M.; Cardona, G.; Cataliotti, L.; Distante, V.; Serio, M.
CORPORATE SOURCE: Clin. Chem. Lab., USL, Florence, Italy

SOURCE: J. Steroid Biochem. (1987), 26(1), 169-71
CODEN: JSTBBK; ISSN: 0022-4731
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Estrogen receptors (ERs) and polyamines (putrescine [110-60-1], spermidine [124-20-9], and spermine [71-44-3]) were examd. in breast tumors from patients who had received tamoxifen **[10540-29-1]** for a few days (5-10) before **surgery**. Women undergoing mastectomy without any preoperatory treatment were selected as the control group. The treatment resulted in a significant lowering of the spermidine-to-spermine ratio. Such a modification was larger in the ER-pos. tumors then in the ER-neg. tumors and seemed to be related to the regression process of the drug-responsive tumors. On the basis of the exptl. data the development of an in vivo tamoxifen-sensitivity test is suggested.

L10 ANSWER 20 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:13141 HCAPLUS
DOCUMENT NUMBER: 106:13141
TITLE: Early alterations at the plasma membrane of breast cancer cell lines in response to estradiol and hydroxytamoxifen.
AUTHOR(S): Pourreau-Schneider, Natalie; Berthois, Yolande; Gandilhon, Philippe; Cau, Pierre; Martin, Pierre Marie; Passerel, Marc
CORPORATE SOURCE: Lab. Histol., Fac. Med., Marseilles, 13326, Fr.
SOURCE: Mol. Cell. Endocrinol. (1986), 48(1), 77-88
CODEN: MCEND6; ISSN: 0303-7207
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The time course of the early stage of estradiol (E2) [50-28-2] and hydroxytamoxifen (OHTAM) **[68047-06-3]** action at the plasma membrane of hormone-responsive MCF and nonresponsive MDA-MB-231 (MDA) breast cancer cell lines was investigated by SEM, electron-probe X-ray microanal., and microelectrophysiol. anal. SEM showed a marked increase in the d. and the length of microvilli (MV) on MCF-7 cells treated with 1 nM estradiol for 1 min. This membrane response disappeared at 5 min. No early effect was obtained with OHTAM, but both compds. produced a similar **surge** of heterogeneous MV at 15 min of treatment. The morphol. change induced by E2 subsided at 60 min, whereas that of OHTAM persisted. X-ray microanal. and computer detn. of peak/background ratios permitted the demonstration that these morphol. alterations were concomitant with a rise in the intracellular level of K+. Microelectrophysiol. anal. showed a sharp transitory decrease in the membrane potential of MCF-7 cells in response to estradiol. In the estrogen-insensitive MDA cells, the hormone did not modify the membrane potential and K levels decreased at 1 and 5 min before increasing again to control levels at minute 15 when MV appeared. With OHTAM, K+ decreased significantly at 60 min of treatment. These initial and transitory changes in surface morphol., paralleled by alterations in K+ level, may be consistent with the occurrence of estrogen membrane receptors on target cells, a new aspect of steroid hormone action.

L10 ANSWER 21 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1986:583914 HCAPLUS
DOCUMENT NUMBER: 105:183914
TITLE: Inhibition of cholesterol and fatty acid synthesis in rats by an estrogen antagonist both in isolated hepatocytes and in vivo
AUTHOR(S): McCune, Sylvia A.; Rimmell, Frank; Hoversland, Roger C.; Jurin, Richard R.
CORPORATE SOURCE: Chicago Med. Sch., Univ. Health Sci., North Chicago, IL, 60064, USA
SOURCE: Biochem. Soc. Trans. (1986), 14(6), 1198
CODEN: BCSTB5; ISSN: 0300-5127
DOCUMENT TYPE: Journal

LANGUAGE: English
AB Treatment of spontaneously **hypertensive** obese rats with the estrogen antagonist tamoxifen [**10540-29-1**] for 3 wk lowered serum cholesterol [57-88-5], serum triglycerides, serum glucose [50-99-7], and body wt. Tamoxifen also inhibited cholesterol formation, fatty acid synthesis, and pyruvate [127-17-3] and acetoacetate [541-50-4] levels in hepatocytes from normal rats; lactate [50-21-5] and .beta.-hydroxybutyrate [300-85-6] levels were increased by tamoxifen, as was the release of glucose. The inhibitory action of tamoxifen om cholesterol and fatty acid formation by hepatocytes was not changed by the addn. of estrogen, suggesting that it acted at some specific step in hepatic lipid synthesis and not at the estrogen receptor.

L10 ANSWER 22 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:465228 HCAPLUS
DOCUMENT NUMBER: 103:65228
TITLE: Effect of the estrogen antagonist, tamoxifen, on development of glomerulosclerosis in the Cohen diabetic rat
AUTHOR(S): Cohen, A. M.; Rosenmann, E.
CORPORATE SOURCE: Isot. Lab. Endocr. Res., Hadassah Univ. Hosp., Jerusalem, 91120, Israel
SOURCE: Diabetes (1985), 34(7), 634-8
CODEN: DIAEAZ; ISSN: 0012-1797
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Long-term administration of the estrogen antagonist, tamoxifen [**10540-29-1**] to female, Cohen **diabetic** rats caused a decrease in the incidence of glomerulosclerosis, 12.5% as compared with 58.3% in control, untreated, **diabetic** female rats. This change in incidence was correlated with a corresponding decrease in plasma estradiol [50-28-2] and cholesterol [57-88-5] levels, but not with changes in oral glucose tolerance or insulin response. A similar correlation between decreased incidence of glomerulosclerosis and a decrease in plasma estradiol was previously noted in ovariectomized animals.
IT **10540-29-1**
RL: BIOL (Biological study)
(kidney glomerulosclerosis attenuation by, in **diabetes**, cholesterol and estradiol of blood plasma in relation to)

L10 ANSWER 23 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:448403 HCAPLUS
DOCUMENT NUMBER: 103:48403
TITLE: Antiestrogen inhibition of estradiol-induced alterations in hypothalamic noradrenaline turnover
AUTHOR(S): Hiemke, C.; Poetz, B.; Ghraf, R.
CORPORATE SOURCE: Inst. Physiol. Chem., Essen Univ. Clin., Essen, D-4300, Fed. Rep. Ger.
SOURCE: J. Endocrinol. (1985), 106(1), 37-42
CODEN: JOENAK; ISSN: 0022-0795
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Long-term (4-6 wk) ovariectomized rats were injected with either estradiol (I) [50-28-2] (20 .mu.g s.c.) or monohydroxytamoxifen (MTAM) [**65213-48-1**] (0.2 mg i.p.) plus I. I was administered at 12:00 h on day 0 and MTAM was given immediately before I, followed by further injections twice daily to maintain sufficiently high antiestrogen levels. When given alone, I reduced the serum levels of LH [9002-67-9] during the morning (08:00-09:00 h) and afternoon (17:30-18:30 h) of day 3 after priming. The feedback actions of I on LH release were accompanied by time-dependent alterations of noradrenaline [51-41-2] turnover in the preoptic-anterior hypothalamic brain area (POAH). On day 3 after priming the noradrenaline turnover rate was reduced in the morning and increased in the afternoon. The increase correlated with an enhanced sensitivity of the LH secretory system to progesterone. The antiestrogen MTAM blocked

the I-induced sensitization of LH release to the stimulatory action of progesterone and interfered with the stimulatory long-term effect of I on hypothalamic noradrenaline turnover. Apparently, the I-induced afternoon increase of noradrenaline turnover in the POAH represents a prerequisite for the induction of LH **surges**. The stimulatory effect of I on hypothalamic noradrenaline turnover seems to be mediated by a classical estrogen receptor mechanism.

IT **65213-48-1**
RL: BIOL (Biological study)
(estradiol stimulation of noradrenaline turnover in hypothalamus inhibition by, LH **surge** in relation to)

L10 ANSWER 24 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:154801 HCAPLUS
DOCUMENT NUMBER: 102:154801
TITLE: Prophylaxis and therapy for coronary heart diseases by lowering the estrogen level
INVENTOR(S): Schulze, Paul Eberhard; Kerb, Ulrich
PATENT ASSIGNEE(S): Schering A.-G. , Fed. Rep. Ger.
SOURCE: Ger. Offen., 9 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3323321	A1	19850103	DE 1983-3323321	19830624
WO 8500107	A1	19850117	WO 1984-DE137	19840619
W: JP, US				
RW: DE, FR, GB, NL				
JP 60501656	T2	19851003	JP 1984-502536	19840619
EP 179062	A1	19860430	EP 1984-902507	19840619
R: DE, FR, GB, NL				

PRIORITY APPLN. INFO.: DE 1983-3323321 19830624
WO 1984-DE137 19840619

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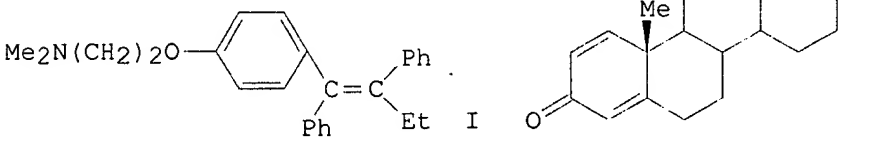

AB **Coronary** heart disease in men is treated by administration of an antiestrogen, such as tamoxifen (I) [**10540-29-1**], or an aromatase inhibitor, such as testololactone (II) [4416-57-3], in daily doses of 10-200 or 50-1000 mg, resp. Tablets were prepd. contg. II 100, lactose 80.5, cornstarch 39.5, PVP 2.5, Aerosil 2.0, and Mg stearate 0.5 mg.

IT **10540-29-1**
RL: BIOL (Biological study)
(pharmaceuticals, for **coronary** heart disease treatment, in men)

L10 ANSWER 25 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:132798 HCAPLUS
DOCUMENT NUMBER: 100:132798
TITLE: Antiestrogenic effects of tamoxifen on mammary gland

and hypophysis in female rats
AUTHOR(S): Goetze, Stephan; Nishino, Yukishige; Neumann, Friedmund
CORPORATE SOURCE: Res. Lab., Schering A.-G., Berlin, 1000/65, Fed. Rep. Ger.
SOURCE: Acta Endocrinol. (Copenhagen) (1984), 105(3), 360-70
CODEN: ACENA7; ISSN: 0001-5598
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Adult ovariectomized rats were treated for 14 days with estradiol (E2) [50-28-2] (15 .mu.g E2 benzoate (E2B)/kg/day) E2B + progesterone (PRO) [57-83-0] 15 mg/kg/day) for induction of mammary gland parenchymal stimulation. Histol. examn. and whole mount prepn. demonstrated that ductal growth in the mammary gland after E2B treatment was completely antagonized by tamoxifen (TAM) [**10540-29-1**] (0.5 mg/kg/day). Parallel DNA concns. in the mammary gland decreased to controllevels in TAM (0.5, 5, and 15 mg/kg/day) response. E2B-induced hyperprolactinemia in the forenoon (basal secretion was equally reduced by TAM (0.5, 5, and 15 mg/kg/day)). In the afternoon, when prolactin (Prl) [9002-62-4] secretion is at its max., 0.5 mg TAM kg/day did not abolish the Prl **surge**, but TAM at 5 and 15 mg/kg/day reduced serum Prl concns. in a dose-related manner. Immunoperoxidase staining of Prl cells in the pars distalis of the hypophysis indicated that adaptive hypertrophy and signs of hypersecretion after E2 were abolished by TAM (5 mg/kg/day). Luteotropic cells clearly showed cellular atrophy, regression, and secretory inactivity. Maximal tubulo-alveolar mammary parenchymal stimulation in rats treated with E2B-PRO was slightly inhibited by TAM (0.5 mg/kg/day). Histol. showed a small disseminated parenchymal islet. DNA concns. were partially decreased by the antiestrogen although serum Prl concns. were decreased to control levels. Secretory activity of Prl cells was reduced by TAM (0.5 mg/kg/day). In E2B-PRO-treated rats lisuride [18016-80-3] had poor inhibitory activity on Prl levels and none on DNA concns. in the mammary gland. Combined treatment with TAM and lisuride decreased DNA concns. in the mammary gland compared to animals which received E2B-PRO. Prl levels were also at a min. Mammary histol. showed only slight tubulo-but no tubulo-alveolar activation. Lutetropic cells in the pituitary gland stained by the immunoperoxidase technique appeared regressive, shrunken, and atrophied.

L10 ANSWER 26 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1983:569921 HCAPLUS
DOCUMENT NUMBER: 99:169921
TITLE: Effect of estrogen and placental lactogen on lactogenesis in pregnant rats
AUTHOR(S): Bussmann, L. E.; Koninckx, A.; Deis, R. P.
CORPORATE SOURCE: Lab. Reprod. Lactancia, Mendoza, 5500, Argent.
SOURCE: Biol. Reprod. (1983), 29(3), 535-41
CODEN: BIREBV; ISSN: 0006-3363
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The removal of the corpora lutea or ovariectomy on day 18 of pregnancy induced a rise in serum prolactin [9002-62-4] 24 h after **surgery** with a rapid decline to control values 4 h after the **surge**, only in the ovariectomized group. When hysterectomy was performed in addn. to luteectomy or ovariectomy a similar rise in prolactin was obtained. Lactose synthetase [9030-11-9] activity in mammary tissue was significantly higher in the luteectomized and luteectohysterectomized rats when compared with ovariectomized, ovariohysterectomized rats and the sham-operated group. Estrogen treatment 12 h after ovariectomy increased serum prolactin and lactose synthetase activity to values similar to those measured in luteectomized rats, but this increase was significantly greater when compared with the ovariectomized-nontreated group. Treatment with tamoxifen [**10540-29-1**] did not decrease serum prolactin in the luteectomized rats but lactose synthetase was reduced to values similar to that obtained in ovariectomized rats. Treatment with 2-bromo-alpha-ergocryptine-mesylate (CB-154) prevented the rise in serum

prolactin in the ovariectomized, luteectomized and luteectohysterectomized groups, but lactose synthetase activity was lowered to control values (sham-operated rats) only in the luteectohysterectomized rats. Apparently, rat placental lactogen [9035-54-5] in the absence of prolactin and progesterone induces lactose synthesis. Estrogen facilitates prolactin but not placental lactogen action on lactose synthetase activity.

L10 ANSWER 27 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1983:516421 HCAPLUS
DOCUMENT NUMBER: 99:116421
TITLE: Effects of tamoxifen on concentrations of luteinizing hormone and follicle-stimulating hormone in the plasma of ovariectomized ewes
AUTHOR(S): Clarke, I. J.
CORPORATE SOURCE: Med. Res. Cent., Prince Henry's Hosp., Melbourne, 3004, Australia
SOURCE: J. Endocrinol. (1983), 99(1), 23-9
CODEN: JOENAK; ISSN: 0022-0795
DOCUMENT TYPE: Journal
LANGUAGE: English
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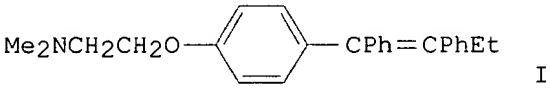

I

AB Tamoxifen (I) [**10540-29-1**] reduced plasma LH [9002-67-9] and FSH [9002-68-0] levels in ovariectomized ewes, suggesting it is an estrogen agonist in the sheep pituitary gland. A partial estrogen antagonist action of I is also suggested by its ability to block the estrogen-induced LH **surge** in some ovariectomized ewes. The I-induced lowering of plasma gonadotropin levels in ovariectomized ewes could result from action via estrogen receptors or by central nervous system, nonestrogen receptor-mediated effects.

L10 ANSWER 28 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1983:432846 HCAPLUS
DOCUMENT NUMBER: 99:32846
TITLE: Effects of a new antiestrogen, keoxifene (LY156758), on growth of carcinogen-induced mammary tumors and on LH and prolactin levels
AUTHOR(S): Clemens, James A.; Bennett, D. R.; Black, L. J.; Jones, C. D.
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Life Sci. (1983), 32(25), 2869-75
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
AB LY156758 (I) [82640-04-8] administration (1-20 mg/kg/day, orally) inhibited the growth of 7,12-dimethylbenzanthracene (DMBA)-induced mammary tumors in rats. The degree of inhibition of mammary tumor growth was similar to that obsd. with tamoxifen [**10540-29-1**] treatment. In ovariectomized (OVX) rats daily treatment with 2 .mu.g of estradiol [50-28-2] as estradiol benzoate resulted in low serum LH [9002-67-9] and prolactin [9002-62-4] levels in the morning followed by greatly elevated levels in the late afternoon. I, but not tamoxifen, prevented the lowering of serum LH levels by estradiol in the morning, while tamoxifen, but not I, blocked the afternoon elevation of serum LH. The afternoon increases in serum prolactin were antagonized to a greater extent by taxomifen than by I. The increase in uterine wt. after estradiol benzoate was antagonized to a significantly greater extent with I than with

taxomifen, and in intact female rats I produced a significantly greater regression of the mammary gland than did tamoxifen. Apparently, I has a greater antiestrogenic effect tamoxifen on estrogen target organs, but the greater degree of antiestrogenicity is not reflected in an enhanced antitumor effect. The lack of an enhanced antitumor effect may be the result of the lesser ability of I to antagonize the estradiol-induced **surges** of prolactin, or the partial estrogenic effects of tamoxifen may play a role in its antimammary tumor effects.

L10 ANSWER 29 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1983:83792 HCAPLUS
DOCUMENT NUMBER: 98:83792
TITLE: Estrogen responsiveness of progestin receptor induction in the pituitary, preoptic-hypothalamic brain, and uterus of neonatally estrogenized female rats
AUTHOR(S): Ghraf, Ruediger; Kirchhoff, Josef; Gruenke, Wolfgang; Reinhardt, Walter; Ball, Peter; Knuppen, Rudolf
CORPORATE SOURCE: Inst. Physiol. Chem., Universitaetsklin. Essen, Essen, D-4300, Fed. Rep. Ger.
SOURCE: Brain Res. (1983), 258(1), 133-8
CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Female rats were defeminized by neonatal treatment with estradiol [50-28-2], RU 2858 [34816-55-2], ICI 79280 [**65213-48-1**], or the dibenzoate esters of the catechol estrogens, 2-hydroxyestradiol [362-05-0] and 4-hydroxyestradiol [5976-61-4]. When ovariectomized as adults and primed with estradiol, all these rats demonstrated a deficient LH [9002-67-9] response to progesterone [57-83-0] administration. However, estrogen responsiveness of progestin receptor induction was unimpaired in both the pituitary gland, the preoptic-hypothalamic brain, and the uterus. Thus, the lack of a neuroendocrine progesterone response, such as induction of LH **surges**, in estrogen-primed, neonatally defeminized rats cannot be attributed to estrogen unresponsiveness of progestin receptor induction in the pituitary gland and preoptic-hypothalamic brain.

L10 ANSWER 30 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1983:28144 HCAPLUS
DOCUMENT NUMBER: 98:28144
TITLE: Enzymic properties of prostaglandin synthetase from human breast cancer. Direct effects of estrogens and antiestrogens
AUTHOR(S): Rolland, P. H.; Martin, P. M.
CORPORATE SOURCE: Lab. Recept. Horm., Fac. Med. Marseille, Marseille, F-13326, Fr.
SOURCE: Rev. Endocr.-Relat. Cancer, Suppl. (1982), 9, 69-74
CODEN: RECSDC; ISSN: 0260-0889
DOCUMENT TYPE: Journal
LANGUAGE: English
AB prostaglandin synthetase [9055-65-6] Studied in a microsomal prepn. from **surgical** samples of human breast cancer had an apparent Km of 4.76 .times. 10-5M and Vmax of 3.6 mmol/mg protein/min and a max. velocity of PGE2 [363-24-6] formation at 0.8-7.5 mg microsomal protein/mL incubation mixt. The natural estrogen hormones stimulated prostaglandin synthetase activity with estradiol [50-28-2] being the most potent, whereas antiestrogens such as tamoxifen [**10540-29-1**] and its metabolites exhibited stimulatory or inhibitory effects depending on the chem. nature and concn. of the antiestrogen. A comparison of the antiestrogenic potency of tamoxifen and its metabolites as measured by their ability to displace R 2858 [34816-55-2] binding and the effects of the antiestrogens on prostaglandin synthetase activity showed that the effects of the antiestrogens on prostaglandin synthetase activity can not be dissocd. from their antiestrogenic activities.

L10 ANSWER 31 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1981:526469 HCAPLUS
DOCUMENT NUMBER: 95:126469
TITLE: Role of hormones in the growth and regression of human breast cancer cells (MCF-7) transplanted into athymic nude mice
AUTHOR(S): Shafie, Samir M.; Grantham, Flora H.
CORPORATE SOURCE: Lab. Pathophysiol., Natl. Cancer Inst., Bethesda, MD, 20205, USA
SOURCE: JNCI, J. Natl. Cancer Inst. (1981), 67(1), 51-6
CODEN: JJIND8; ISSN: 0198-0157
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The hormonal environments required by human breast cancer cells MCF-7 to produce solid tumors in nude mice mammary fat pads are described. Tumors failed to develop in ovariectomized mice or in mice made **diabetic** with streptozotocin. A 100% incidence of tumors was obtained in mice that were either hypophysectomized or made **diabetic** but received injections of 0.2 IU insulin [9004-10-8]/day/mouse. A 100% incidence of tumors was also obtained in ovariectomized mice that received 17.beta.-estradiol valerate [979-32-8] in the form of a pellet placed s.c. in the interscapular region. Palpable tumors also developed in ovariectomized mice treated with prolactin [9002-62-4], perphenazine [58-39-9], estrone [53-16-7], or estriol [50-27-1] but no takes were obsd. in ovariectomized mice treated with progesterone [57-83-0], 5.alpha.-dihydrotestosterone [521-18-6], or hydrocortisone [50-23-7]. Growth of the MCF-7 tumor was stimulated 5-6-fold in both intact and hypophysectomized mice given the 17.beta.-estradiol pellets. Removal of the 17.beta.-estradiol pellets from tumor-bearing ovariectomized mice failed to induce tumor regression. Tumors that continued to grow in ovariectomized mice deprived of 17.beta.-estradiol regressed by .gtoreq.50% when tamoxifen [**10540-29-1**] was injected. When tamoxifen was substituted by dibutyryl cAMP [362-74-3] .+-. theophylline, tumor growth arrest was obsd. Streptozotocin-induced **diabetes** in tumor-bearing mice always resulted in complete tumor regression.

L10 ANSWER 32 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1980:51653 HCAPLUS
DOCUMENT NUMBER: 92:51653
TITLE: Binding of drugs to human serum albumin: XI. The specificity of three binding sites as studied with albumin immobilized in microparticles
AUTHOR(S): Sjoeholm, Ingvar; Ekman, Bo; Kober, Anita; Ljungstedt-Paahlman, Ingrid; Seiving, Birgitta; Sjoedin, Torgny
CORPORATE SOURCE: Biomed. Cent., Univ. Uppsala, Uppsala, S-751 23, Swed.
SOURCE: Mol. Pharmacol. (1979), 16(3), 767-77
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human serum albumin was immobilized in spherical, macroporous microparticles of polyacrylamide of .apprx.1 .mu.m in diam. with retention of its native properties. Since diazepam [439-14-5], digitoxin [71-63-6] and warfarin [81-81-2] independently bind to albumin, the labeled compds. were used as markers of 3 sep., discrete binding sites on albumin. The capacity of .apprx.140 drugs and other compds. to affect the binding of the radioactively labeled markers was then studied. Some drugs, e.g. antirheumatic drugs of the isopropionic acid-type, some **antidiabetic** agents, penicillin derivs., and benzodiazepines efficiently displaced diazepam. Other drugs, e.g., some diuretics, S drugs, and butazone derivs. displaced warfarin. Displacement of digitoxin was less common. In some cases the binding of the markers was improved, e.g., tamoxifen [**10540-29-1**] increased the binding of warfarin. Both competitive and allosteric mechanisms are responsible for the changed binding of the markers. The results suggest the presence of more than the 3 binding sites for drugs on the albumin surface studied with diazepam,

digitoxin and warfarin.

L10 ANSWER 33 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1978:788 HCAPLUS
DOCUMENT NUMBER: 88:788
TITLE: Abolition of the pre-implantation surge of plasma estrogens in mice with tamoxifen
AUTHOR(S): Bloxham, P. A.; Pugh, D. M.; Sharma, S. C.
CORPORATE SOURCE: Dep. Pharmacol., Trinity Coll., Dublin, Ire.
SOURCE: IRCS Med. Sci.: Libr. Compend. (1977), 5(9), 432
CODEN: IRLCDZ
DOCUMENT TYPE: Journal
LANGUAGE: English
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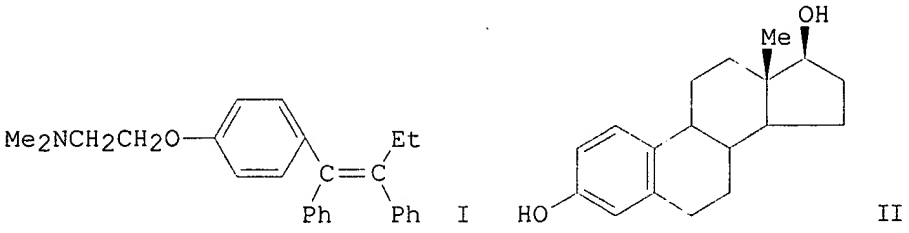

AB In female mice, tamoxifen (I) [**10540-29-1**] (1 mg/kg, orally) administered at 40-4 h postcoitum abolished the plasma estradiol (II) [50-28-2] **surge** at 84 h postcoitum obsd. in untreated control mice. Apparently, the antiestrogenic effect of I in preventing implantation depends on its ability to abolish the day 4 endogenous estrogen **surge**.

L10 ANSWER 34 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1977:463274 HCAPLUS
DOCUMENT NUMBER: 87:63274
TITLE: Influence of current modes of treatment in male infertility on the hypothalamo-pituitary testicular function
AUTHOR(S): Comhaire, F.; Dhondt, M.
CORPORATE SOURCE: Acad. Ziekenhuis, Ghent, Belg.
SOURCE: Releasing Factors Gonadotropic Horm. Male Female Steril. - Radioimmunoassays Diagn. Tools Gynecol. Androl., [Int. Symp.] (1975), Meeting Date 1974, 117-32. Editor(s): Schellen, Ton M. C. M. Eur. Press: Ghent, Belg.
CODEN: 35MBA5
DOCUMENT TYPE: Conference
LANGUAGE: English
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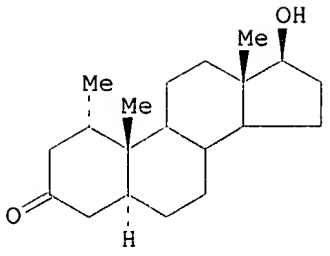

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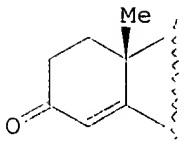

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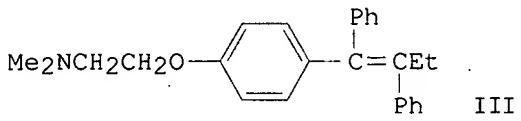

III

AB In male patients with hypergonadotropic hypogonadism, mesterolone (I) [1424-00-6] (150 mg/day, orally) suppressed both plasma LH [9002-67-9] and testosterone (II) [58-22-0]. The plasma LH response to LH-releasing hormone (LH-RH) [9034-40-6] did not show definite changes, whereas plasma FSH [9002-68-0] levels either basal or after LH-RH showed no consistent variations. In patients with idiopathic oligospermia, treatment with tamoxifen (III) [**10540-29-1**] (20, 40, or 60 mg/day, orally) increased plasma II from a basal level of 468 ng/100 mL to 1004 ng/100 mL. The increase in plasma II was evident already after 5 days of treatment and was maintained during the continuous intake of the drug for up to 5 months. Plasma LH level, after treatment with III, increased from 9.7 to 14.4 mIU/mL. In varicocele patients, treated with corrective **surgery** there was a correlation between the quant. of spermatogenic activity and both LH and FSH secretion. In these same patients, there was also a correlation both between LH and FSH response to LH-RH, and between the basal LH and FSH levels. Neither LH nor FSH response to LH-RH were correlated with plasma II level. III may be useful for pituitary-gonadotropic stimulation in patients with a normally responsive hypothalamo-pituitary system.

L10 ANSWER 35 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1976:587091 HCAPLUS
DOCUMENT NUMBER: 85:187091
TITLE: Effect of the antiestrogen tamoxifen on plasma levels of luteinizing hormone, follicle-stimulating hormone, prolactin, estradiol and progesterone in normal premenopausal women
AUTHOR(S): Groom, G. V.; Griffiths, K.
CORPORATE SOURCE: Tenovus Inst. Cancer Res., Welsh Natl. Sch. Med., Cardiff, Wales
SOURCE: J. Endocrinol. (1976), 70(3), 421-8
CODEN: JOENAK
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Administration of tamoxifen [**10540-29-1**] (20 mg/day, orally) for 5 or 10 days of the follicular phase of the menstrual cycle in healthy women increased plasma estradiol [50-28-2] levels 2- to 8-fold, esp. during midcycle and midluteal hormone peaks, but had no effect on the overall length of the cycle or on the time of occurrence of the mid-cycle gonadotropin **surge**. Plasma prolactin [9002-62-4] levels were decreased by tamoxifen at midcycle, but not during the remainder of the cycle. Secretion of LH [9002-67-9], FSH [9002-68-0], and progesterone [57-83-0] was hardly affected by tamoxifen. Tamoxifen may act directly on the ovary to stimulate estradiol release without gonadotropin stimulation; alternatively it may augment ovarian stimulation by normal gonadotropin concns. by reducing prolactin concn.

L10 ANSWER 36 OF 40 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1976:130563 HCAPLUS
DOCUMENT NUMBER: 84:130563
TITLE: Effects of hypophysectomy, ovariectomy, and cycloheximide on specific binding sites for lactogenic hormones in rat liver
AUTHOR(S): Kelly, Paul A.; Posner, Barry I.; Friesen, Henry G.
CORPORATE SOURCE: Fac. Med., Univ. Manitoba, Winnipeg, Manitoba, Can.
SOURCE: Endocrinology (1975), 97(6), 1408-15
CODEN: ENDOAO
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the present studies growth hormone (GH) [9002-72-6] was used to study binding sites specific for lactogenic hormones in liver membranes. In male rats, a single injection of 2 mg estradiol valerate [979-32-8] induced these binding sites. The induction was maximal by 9-12 days and was dose-dependent. Ovariectomy reduced the specific binding of GH from 9.7 .+-. 0.7% in shamoperated to 6.9 .+-. 0.3% in exptl. rats without a change in affinity. Fluctuations in specific binding of GH were obsd. at different stages of the estrous cycle. Binding at estrus and diestrus I was significantly greater than at diestrus II and proestrus. The disappearance of binding sites following hypophysectomy was rapid, declining from 13.2 .+-. 1.2% in intact rats to 6.0 .+-. 0.8% and 2.2 .+-. 0.4% 14 and 48 hr resp., after **surgery**. In contrast, binding of insulin [9004-10-8] was slightly increased after hypophysectomy. Antiestrogens (clomiphene [911-45-5], ICI 46,474 [**10540-29-1**], and nafoxidine [1845-11-0]) prevented the induction of binding sites in male rats given estradiol (E2). A single injection of 200 .mu.g cycloheximide 11 days after an injection of 2 mg E2-valerate reduced binding by more than 90% in 3 hr with a return to control levels by 48 hr. The maximal decline in insulin binding was 54% during this entire period. These studies suggest that endogenous estrogen plays a role in regulating hepatic binding sites for lactogenic hormones. The level of these binding sites is critically dependent on the presence of an intact pituitary. The possible rapid turnover of these sites suggests that regulatory influences at the tissue level may have an important role in modulating hormone action.

L10 ANSWER 37 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1976:99699 HCAPLUS
DOCUMENT NUMBER: 84:99699
TITLE: Estrogen synthesis during delayed implantation in the rat
AUTHOR(S): Watson, John; Alam, M.
CORPORATE SOURCE: Dep. Biochem., Univ. Strathclyde, Glasgow, Scot.
SOURCE: Contraception (1976), 13(1), 101-7
CODEN: CCPTAY
DOCUMENT TYPE: Journal
LANGUAGE: English
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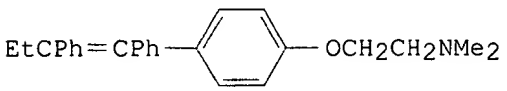

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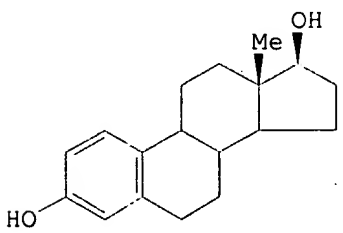


II

AB Oral administration of Tamoxifen (I) [**10540-29-1**] (0.1 mg/kg), a postcoital contraceptive, to rats on day 2 of pregnancy inhibited in vitro ovarian estradiol (II) [50-28-2] synthesis on days 2 and 3 of pregnancy and inhibited such synthesis on day 4 of pregnancy. I-treated rats had decreased and increased plasma II levels on days 3 and 4 of pregnancy, resp. Thus, delay of implantation by I may be mediated by inhibition of ovarian II synthesis which prevents the normal plasma II **surge** late on day 3 of pregnancy in rats.

L10 ANSWER 38 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1975:453758 HCAPLUS
DOCUMENT NUMBER: 83:53758
TITLE: Inhibition of estrogen-stimulated prolactin release by antiestrogens
AUTHOR(S): Jordan, V. C.; Koerner, S.; Robison, C.
CORPORATE SOURCE: Worcester Found. Exp. Biol., Shrewsbury, Mass., USA
SOURCE: J. Endocrinol. (1975), 65(1), 151-2
CODEN: JOENAK
DOCUMENT TYPE: Journal
LANGUAGE: English
AB ICI 46474 [**10540-29-1**] and ethamoxytriphetol [67-98-1] (50 .mu.g and 5 mg resp. daily for 7 days, s.c.) reduced the increases in plasma prolactin [9002-62-4] concn. and uterine wt. induced by estradiol in ovariectomized rats. The 2 antiestrogens also reduced the proestrus **surge** in plasma prolactin concn. and uterine wt.

L10 ANSWER 39 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1975:438077 HCAPLUS
DOCUMENT NUMBER: 83:38077
TITLE: Plasma hormones and pituitary luteinizing hormone in the rat during the early stages of pregnancy and after postcoital treatment with tamoxifen (ICI 46,474)
AUTHOR(S): Watson, J.; Anderson, F. B.; Alam, M.; O'Grady, J. E.; Heald, P. J.
CORPORATE SOURCE: Dep. Biochem., Univ. Strathclyde, Glasgow, Scot.
SOURCE: J. Endocrinol. (1975), 65(1), 7-17
CODEN: JOENAK
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB The plasma levels of estradiol-17.beta. (I) [50-28-2], progesterone (II) [57-83-0], and LH [9002-67-9] and pituitary LH levels were measured during the 1st 6 days of pregnancy in normal rats and in rats receiving Tamoxifen (III) [**10540-29-1**] (0.1 or 0.2 mg/kg orally on day 2). The 20- to 24-hr delay in implantation induced by 0.1 mg III/kg was accompanied by a 20-hr delay in the increased formation of I, which, in normal rats, peaked about midnight on day 3 rather than late on day 4. The higher, implantation-inhibiting dose of III prevented the increase in plasma I and affected LH levels, but neither III dose affected plasma II. The antifertility activity of III may result partially from its inhibition of I formation from II. The estrogen **surge** in early pregnancy probably results from increased FSH release rather than increased LH release.

L10 ANSWER 40 OF 40 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1975:149669 HCAPLUS
DOCUMENT NUMBER: 82:149669
TITLE: Effect of ICI 46474 (Tamoxifen) on hormone concentrations during early pregnancy in the rat
AUTHOR(S): Watson, John; Alam, Mahmood; Anderson, Frank B.; Heald, Peter J.
CORPORATE SOURCE: Dep. Biochem., Univ. Strathclyde, Glasgow, Scot.
SOURCE: Biochem. Soc. Trans. (1974), 2(5), 982-3
CODEN: BCSTB5

DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB ICI 46474 (I) [**10540-29-1**] (0.1 mg/kg) delayed the **surge** in circulating estradiol [50-28-2] levels, normally obsd. on day 3 of pregnancy, by 22 hr, and at 0.2 mg/kg delayed this **surge** for at least day 6, indicating that I delays implantation by altering estradiol release. This effect was not mediated by LH.

=> select hit rn l9 1-52
E1 THROUGH E11 ASSIGNED

=> select hit rn l10 1-40
E12 THROUGH E15 ASSIGNED

=> fil reg
FILE 'REGISTRY' ENTERED AT 21:08:38 ON 27 APR 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2001 American Chemical Society (ACS)

STRUCTURE FILE UPDATES: 26 APR 2001 HIGHEST RN 333301-66-9
DICTIONARY FILE UPDATES: 26 APR 2001 HIGHEST RN 333301-66-9

TSCA INFORMATION NOW CURRENT THROUGH January 11, 2001

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

=>

=>

=> d his l12

(FILE 'HCAPLUS' ENTERED AT 20:59:10 ON 27 APR 2001)
SELECT HIT RN L9 1-52
SELECT HIT RN L10 1-40

FILE 'REGISTRY' ENTERED AT 21:08:38 ON 27 APR 2001
L12 11 S E1-E15

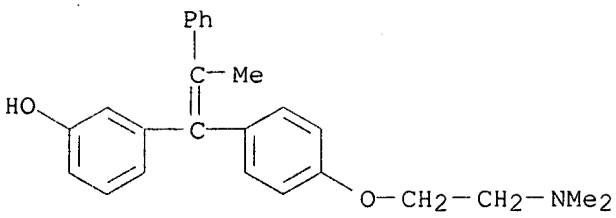
=>
=>

=> d ide can l12 1-11

L12 ANSWER 1 OF 11 REGISTRY COPYRIGHT 2001 ACS
RN **161401-02-1** REGISTRY
CN Phenol, 3-[1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenyl-1-propenyl]-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (salt) (9CI) (CA INDEX NAME)
MF C25 H27 N O2 . C6 H8 O7
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

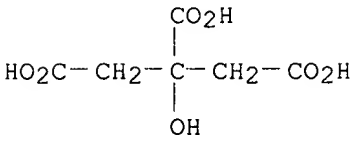
CM 1

CRN 161400-98-2
CMF C25 H27 N O2



CM 2

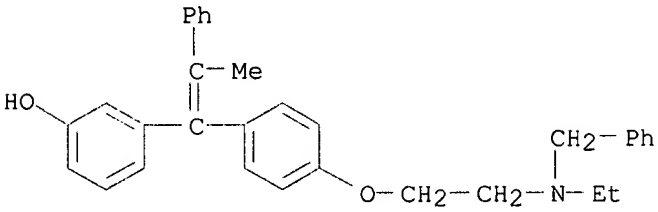
CRN 77-92-9
CMF C6 H8 O7



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 122:151384

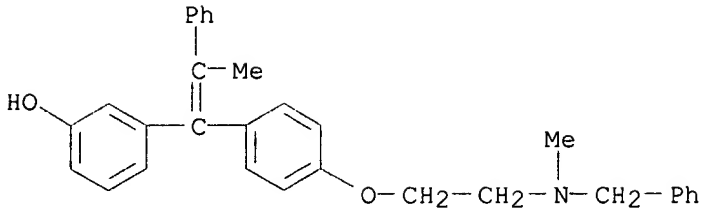
L12 ANSWER 2 OF 11 REGISTRY COPYRIGHT 2001 ACS
RN **161401-01-0** REGISTRY
CN Phenol, 3-[1-[4-[2-[ethyl(phenylmethyl)amino]ethoxy]phenyl]-2-phenyl-1-propenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C32 H33 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 122:151384

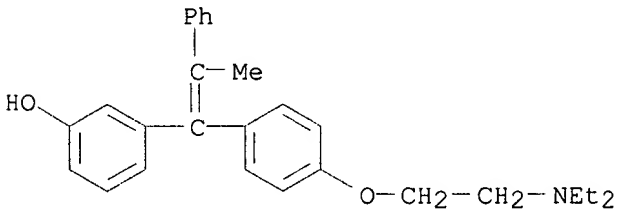
L12 ANSWER 3 OF 11 REGISTRY COPYRIGHT 2001 ACS
RN **161401-00-9** REGISTRY
CN Phenol, 3-[1-[4-[2-[methyl(phenylmethyl)amino]ethoxy]phenyl]-2-phenyl-1-propenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C31 H31 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 122:151384

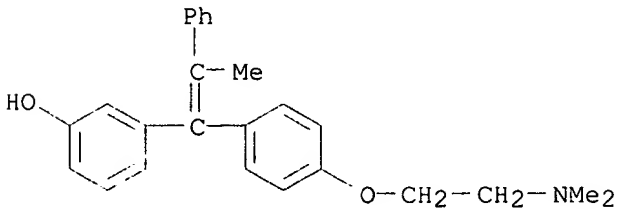
L12 ANSWER 4 OF 11 REGISTRY COPYRIGHT 2001 ACS
RN **161400-99-3** REGISTRY
CN Phenol, 3-[1-[4-[2-(diethylamino)ethoxy]phenyl]-2-phenyl-1-propenyl]-(9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C27 H31 N O2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 122:151384

L12 ANSWER 5 OF 11 REGISTRY COPYRIGHT 2001 ACS
RN **161400-98-2** REGISTRY
CN Phenol, 3-[1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenyl-1-propenyl]-(9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C25 H27 N O2
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

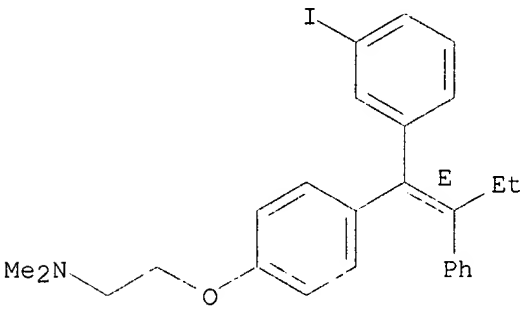


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 122:151384

L12 ANSWER 6 OF 11 REGISTRY COPYRIGHT 2001 ACS
RN **116057-76-2** REGISTRY
CN Ethanamine, 2-[4-[(1E)-1-(3-iodophenyl)-2-phenyl-1-butenyl]phenoxy]-N,N-dimethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethanamine, 2-[4-[1-(3-iodophenyl)-2-phenyl-1-butenyl]phenoxy]-N,N-dimethyl-, (E)-
FS STEREOSEARCH
MF C26 H28 I N O
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Double bond geometry as shown.



5 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:202697

REFERENCE 2: 129:76502

REFERENCE 3: 126:139887

REFERENCE 4: 111:214170

REFERENCE 5: 109:110011

L12 ANSWER 7 OF 11 REGISTRY COPYRIGHT 2001 ACS
RN **82413-20-5** REGISTRY
CN Phenol, 3-[(1E)-1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenyl-1-butenyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phenol, 3-[1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenyl-1-butenyl]-, (E)-
OTHER NAMES:
CN 3-Hydroxytamoxifen
CN Droloxifene
CN E-Droloxifene
CN K 060
CN K 060E
CN K 21.060E
FS STEREOSEARCH
MF C26 H29 N O2
CI COM
LC STN Files: ADISINSIGHT, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXLINE, TOXLIT, ULIDAT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

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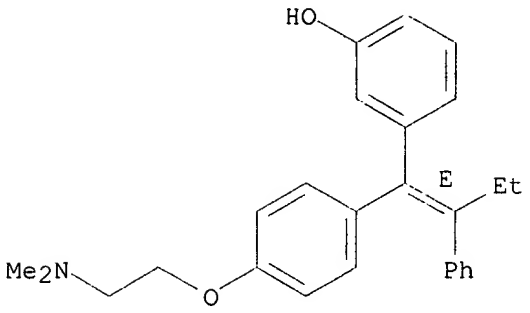

160 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
160 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:261332

REFERENCE 2: 134:261267

REFERENCE 3: 134:220624

REFERENCE 4: 134:202697

REFERENCE 5: 134:178396

REFERENCE 6: 134:173020

REFERENCE 7: 134:172769

REFERENCE 8: 134:95501

REFERENCE 9: 134:81010

REFERENCE 10: 134:33012

L12 ANSWER 8 OF 11 REGISTRY COPYRIGHT 2001 ACS
RN **68047-06-3** REGISTRY
CN Phenol, 4-[(1Z)-1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenyl-1-butenyl]-
(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phenol, 4-[1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenyl-1-butenyl]-,
(Z)-
OTHER NAMES:
CN (Z)-4-Hydroxytamoxifen
CN 4-Hydroxytamoxifen
CN Hydroxytamoxifen
CN ICI 79280
CN trans-4-Hydroxytamoxifen
CN trans-Hydroxytamoxifen
FS STEREOSEARCH
DR **65213-48-1, 72732-26-4, 76276-99-8**
MF C26 H29 N O2
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA,
CAPLUS, CASREACT, CEN, CHEMCATS, CSCHEM, DDFU, DRUGU, EMBASE, IPA,
NIOSHTIC, PHAR, PROMT, RTECS*, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

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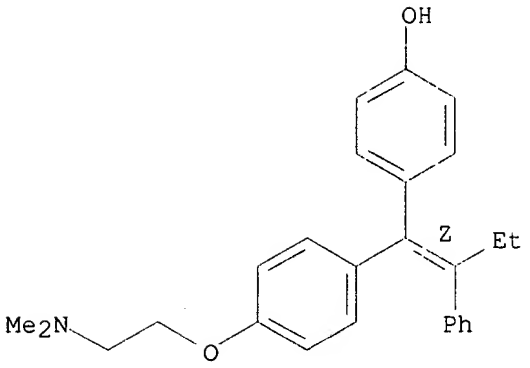

732 REFERENCES IN FILE CA (1967 TO DATE)
24 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
732 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:261332

REFERENCE 2: 134:220629

REFERENCE 3: 134:218100

REFERENCE 4: 134:203558

REFERENCE 5: 134:203354

REFERENCE 6: 134:189063

REFERENCE 7: 134:173195

REFERENCE 8: 134:157824

REFERENCE 9: 134:157316

REFERENCE 10: 134:144207

L12 ANSWER 9 OF 11 REGISTRY COPYRIGHT 2001 ACS
RN **54965-24-1** REGISTRY
CN Ethanamine, 2-[4-[(1Z)-1,2-diphenyl-1-butenyl]phenoxy]-N,N-dimethyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)
OTHER NAMES:
CN ICI 46474
CN Nolvadex
CN Tamoplex
CN Tamox-Puren
CN Tamoxifen citrate
CN Z-Tamoxifen citrate
FS STEREOSEARCH
MF C26 H29 N O . C6 H8 O7
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DIOGENES, DRUGPAT, EMBASE, HSDB*, IMSDIRECTORY, IPA, MRCK*, MSDS-OHS, PIRA, PROMT, RTECS*, TOXLINE, TOXLIT, ULIDAT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

CM 1

CRN 10540-29-1
CMF C26 H29 N O

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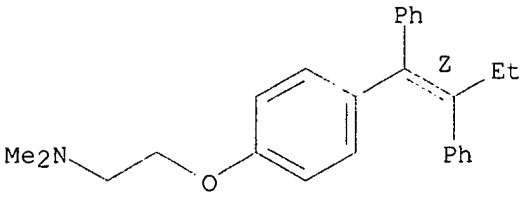
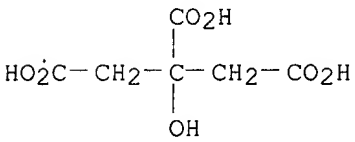


CM 2

CRN 77-92-9
CMF C6 H8 O7



175 REFERENCES IN FILE CA (1967 TO DATE)
175 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:173196

REFERENCE 2: 134:66360

REFERENCE 3: 134:32972

REFERENCE 4: 133:359224

REFERENCE 5: 133:340231

REFERENCE 6: 133:335075

REFERENCE 7: 133:207628

REFERENCE 8: 133:168325

REFERENCE 9: 133:56905

REFERENCE 10: 133:34417

L12 ANSWER 10 OF 11 REGISTRY COPYRIGHT 2001 ACS
RN **13002-65-8** REGISTRY
CN Ethanamine, 2-[4-[(1E)-1,2-diphenyl-1-butenyl]phenoxy]-N,N-dimethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (E)-
CN Ethylamine, 2-[p-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (E)- (8CI)
OTHER NAMES:
CN (E)-Tamoxifen
CN cis-Tamoxifen
FS STEREOSEARCH
MF C26 H29 N O

CI COM
LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CHEMINFORMRX, DRUGPAT, HSDB*, MRCK*, RTECS*, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

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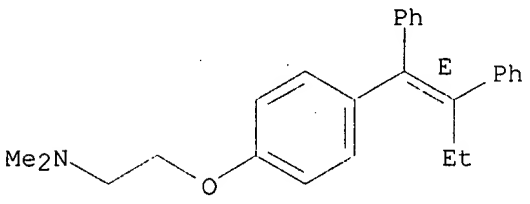


114 REFERENCES IN FILE CA (1967 TO DATE)
114 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:25113

REFERENCE 2: 133:335075

REFERENCE 3: 132:87857

REFERENCE 4: 130:158395

REFERENCE 5: 129:4467

REFERENCE 6: 128:289755

REFERENCE 7: 128:275203

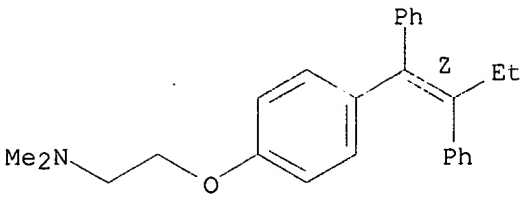
REFERENCE 8: 125:48615

REFERENCE 9: 125:48184

REFERENCE 10: 122:305842

L12 ANSWER 11 OF 11 REGISTRY COPYRIGHT 2001 ACS
RN **10540-29-1** REGISTRY
CN Ethanamine, 2-[4-[(1Z)-1,2-diphenyl-1-butenyl]phenoxy]-N,N-dimethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)-
CN Ethylamine, 2-[p-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)- (8CI)
OTHER NAMES:
CN ICI 47699
CN Mammaton
CN Tamoxifen
CN trans-Tamoxifen
CN Z-Tamoxifen
FS STEREOSEARCH
MF C26 H29 N O
CI COM
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, EMBASE, HSDB*, IMSDIRECTORY, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PROMT, RTECS*, SPECINFO, TOXLINE, TOXLIT, ULIDAT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Double bond geometry as shown.



3811 REFERENCES IN FILE CA (1967 TO DATE)
114 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3819 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:271284

REFERENCE 2: 134:264273

REFERENCE 3: 134:261560

REFERENCE 4: 134:261267

REFERENCE 5: 134:261198

REFERENCE 6: 134:260884

REFERENCE 7: 134:246961

REFERENCE 8: 134:242619

REFERENCE 9: 134:232552

REFERENCE 10: 134:232087